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Some Methods of Estimating the Inbreeding Coefficient

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INTRODUCTION: POPULATION MODELS

IN A LARGE panmictic population in which the frequency of the allele A_i is q_i, the proportions of the various genotypes in an equilibrium condition are given by the coefficients of the A's in the expression

$$[\sum_i q_iA_i]^2 = \sum_i q_i^2A_iA_i + 2\sum_{i<j} q_iq_jA_iA_j \tag{I}$$

where $\Sigma q_i = 1 (i = 1, 2, \cdots, k)$. This result for multiple alleles was first given by Weinberg (1909, cf. Stern, 1943) and we shall refer to this population as Model I in the subsequent sections. When the gametes are not uniting entirely at random but are correlated, there will be relatively more homozygous individuals in the population than in Model I. If the correlation coefficient between the uniting gametes is F (known as the inbreeding coefficient, Wright, 1921, 1922), the population will consist of (Wright, 1949):

$$\begin{aligned}(1 - F)\,[\sum_i q_iA_i]^2 &+ F\sum_i q_iA_iA_i \\ &= \sum_i [(1-F)q_i^2 + Fq_i]A_iA_i + 2(1-F)\sum_{i<j} q_iq_jA_iA_j\end{aligned} \tag{II}$$

We shall refer to this population as Model II. When $F = 0$, it reduces to (I). Since each zygote may be considered as a unification of a pair of gametes, the zygotic proportions of a population may be written in the form of a $k \times k$ gametic combination table. Thus, Table 1 represents the composition of Model II. The corresponding table for Model I is obvious.

It should be remarked that the parameter F, measuring the degree of association between the uniting gametes, is entirely independent of the gene frequencies. The latter tells us what proportion of each allele there is in the population while the former measures the extent of the association between pairs of the alleles.

The present paper deals with some of the methods of estimating the value of F in Population Model II based upon a random sample of N individuals of which a_{ii} are of the genotype A_iA_i and $2a_{ij}$ are A_iA_j where $\Sigma_i a_{ii} + 2\Sigma_{i<j} a_{ij} =$

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N (Table 2). Let $a_{i1} + a_{i2} + \cdots + a_{ik} = n_i$, the marginal totals of Table 2. The estimation of gene frequencies offers no difficulty. They are estimated usually by $q_i = n_i/N$. In the following sections the sample is assumed to be fairly large.

1. TOTAL PROPORTION OF HETEROZYGOTES

Perhaps the simplest method of estimating F is based upon the total proportion of heterozygotes in a sample. Let this value be H (observed $= 2\Sigma a_{ij}/N$). Let H_0 and H_F denote the total proportions of heterozygotes in Models I and

TABLE 1. GAMETIC CORRELATION OF MODEL II

	A_1	A_2	$\cdots$	A_k	
A_1	$(1-F)q_1^2 + Fq_1$	$(1-F)q_1q_2$	$\cdots$	$(1-F)q_1q_k$	q_1
A_2	$(1-F)q_2q_1$	$(1-F)q_2^2 + Fq_2$	$\cdots$	$(1-F)q_2q_k$	q_2
$\cdot\ \cdot$	$\cdot\ \cdot$	$\cdot\ \cdot$		$\cdot\ \cdot$	$\cdot\ \cdot$
A_k	$(1-F)q_kq_1$	$(1-F)q_kq_2$	$\cdots$	$(1-F)q_k^2 + Fq_k$	q_k
	q_1	q_2	$\cdots$	q_k	1

TABLE 2. OBSERVED NUMBERS OF INDIVIDUALS

	A_1	A_2	$\cdots$	A_k	
A_1	a_{11}	a_{12}	$\cdots$	a_{1k}	n_1
A_2	a_{12}	a_{22}	$\cdots$	a_{2k}	n_2
$\cdot$	$\cdot$	$\cdot$		$\cdot$	$\cdot$
A_k	a_{1k}	a_{2k}	$\cdots$	a_{kk}	n_k
	n_1	n_2	$\cdots$	n_k	N

II, respectively. Thus, $H_0 = 2\Sigma q_iq_j = 1 - \Sigma q_i^2$ and $H_F = 2(1 - F)\Sigma q_iq_j$. It is easy to see that (Wright, 1948)

$$F = \frac{H_0 - H_F}{H_0} \quad \text{or} \quad H_F = H_0(1 - F)$$

regardless of the number of alleles involved. In estimating F we simply substitute the observed H for H_F and calculate the value of H_0 taking $q_i = n_i/N$. Hence, using f to denote the sample estimate of F, we have

$$f = 1 - \frac{H}{H_0} = 1 - \frac{N\sum a_{ij}}{\sum n_in_j}, \qquad (i < j) \quad (1)$$

We shall use this notation throughout the paper.

2. PRODUCT-MOMENT CORRELATION

It may be readily verified that the product-moment correlation coefficient between the gametes of Table 1 is F by assigning *any* arbitrary numerical

values (which need not be at unit steps) to alleles $A_1, A_2, \cdots, A_k$ (Wright 1948). The order of the arrangement of the alleles is immaterial. This is, however, not the case with actual sample numbers. For instance, when $k = 3$, there are three different ways of arranging the sample data and thus three different correlation values could be obtained. It is convenient to assign the values $+1, 0, -1$ to A_1, A_2, A_3, respectively, in which case the correlation coefficient is given by

$$f = \frac{N(a_{11} - 2a_{13} + a_{33}) - (n_1 - n_3)^2}{N(n_1 + n_3) - (n_1 - n_3)^2} \tag{2}$$

Two other similar expressions may be derived by interchanging the subscripts 2 & 3, and 1 & 2. If the sample data are consistent with Model II, the values of the three correlations should not differ to any appreciable extent. Although each of them is a consistent estimate of F, it seems desirable to devise some methods of estimation which are independent of the order of arrangement of the sample numbers and yield a unique estimate. The first method (1) satisfies these conditions; the following are some additional methods.

3. DETERMINANT OF THE GAMETIC CORRELATION MATRIX

If we arrange the zygotic proportions of Model I in the form of a gametic correlation table, it will be found that the determinant formed by the elements of the body of that table is zero. The determinant formed by the elements of Table 1 (Model II) is, however, a simple function of F. Removing the factors in q common to all the elements of each row, adding each of the columns to the first, all of whose elements are then equal to unity, and subtracting the first row from each of the remaining rows, we have

$$q_1 \cdots q_k \begin{vmatrix} (1-F)q_1 + F, & (1-F)q_2, & \cdots & (1-F)q_k \\ (1-F)q_1, & (1-F)q_2 + F, & \cdots & (1-F)q_k \\ \cdot & & & \cdot \\ (1-F)q_1, & (1-F)q_2, & \cdots & (1-F)q_k + F \end{vmatrix}$$

$$= q_1 \cdots q_k \begin{vmatrix} 1 & (1-F)q_2 & \cdots & (1-F)q_k \\ 1 & (1-F)q_2 + F & \cdots & (1-F)q_k \\ \cdot & & & \cdot \\ 1 & (1-F)q_2 & \cdots & (1-F)q_k + F \end{vmatrix}$$

$$= q_1 \cdots q_k \begin{vmatrix} 1 & (1-F)q_2 & (1-F)q_3 & \cdots & (1-F)q_k \\ 0 & F & 0 & \cdots & 0 \\ 0 & 0 & F & \cdots & 0 \\ \cdot & & & & \cdot \\ 0 & 0 & 0 & \cdots & F \end{vmatrix}$$

$$= q_1 \cdots q_k F^{k-1}$$

Therefore, the determinant of the observed numbers (Table 2) divided by the product of its marginal totals will yield an estimate of the $(k - 1)$th power of F; thus,

$$f^{k-1} = \frac{\begin{vmatrix} a_{11} & \cdots & a_{1k} \\ \cdot & & \cdot \\ a_{1k} & \cdots & a_{kk} \end{vmatrix}}{n_1 \times n_2 \times \cdots \times n_k} \tag{3}$$

4. CHI-SQUARE ASSUMING PANMIXIA

The departure between the zygotic proportions of Population Models I and II, as caused by the existence of F, may be measured by the value of Chi-square, using the proportions of (I) as the "expected" and those of (II) as "observed" numbers; thus,

$$\begin{aligned} \chi^2 &= \sum_i \frac{[NFq_i(1 - q_i)]^2}{Nq_i^2} + \sum_{i<j} \frac{[2NFq_iq_j]^2}{2Nq_iq_j} \\ &= NF^2\left\{\sum_i (1 - 2q_i + q_i^2) + 2 \sum_{i<j} q_iq_j\right\} \\ &= NF^2(k - 2 + 1) = NF^2(k - 1). \end{aligned}$$

Therefore, if we take $q_i = n_i/N$ and calculate the zygotic proportions (I) on the assumption of panmixia, the value of Chi-square obtained on comparing them with the observed will give us an estimate of F; viz.,

$$f^2 = \frac{\chi^2}{N(k - 1)} \,. \tag{4}$$

This Chi-square has $k(k + 1)/2 - k = k(k - 1)/2$ degrees of freedom. Note that this is a special case of Tschuprow's coefficient where the numbers of rows and columns of a contingency table are equal. The sampling distribution of f may be obtained by a simple transformation of that of Chi-square. The test of significance of f is equivalent to testing the significance of χ^2. This is the chief advantage of using this method of estimation.

5. PROPORTIONS OF ALLELES IN HOMOZYGOUS CONDITION

Let $z_{ii} = (1 - F)q_i^2 + Fq_i$ denote the proportion of A_iA_i in Model II whose total frequency of allele A_i is q_i. Hence, the proportion of A_i in homozygous condition among all A_i's in the population is z_{ii}/q_i. The sum of such proportions over all alleles is

$$\frac{z_{11}}{q_1} + \frac{z_{22}}{q_2} + \cdots + \frac{z_{kk}}{q_k} = 1 + F(k - 1).$$

In Model I $(F = 0)$, the sum of such proportions is unity. From this consideration the sample estimate of F is obviously

$$f = \frac{1}{k-1}\left\{\sum_i \frac{a_{ii}}{n_i} - 1\right\}. \tag{5}$$

Perhaps this is the simplest method of estimation in the sense that it involves the least arithmetic labor.

6. THE CASE OF TWO ALLELES

Before we discuss some other methods of estimation, it may be well at this stage to examine the important special case of only two alleles. To simplify the notations, we let the observed numbers of A_1A_1, A_1A_2, A_2A_2 in the sample be a, $2b$, c, respectively, where $a + 2b + c = N$, as before. The gametic combination table for this case is given in Table 3.

In applying the first method (1) to this case, it is sufficient to note that $a_{12} = b$. In applying (2), we put $a_{13} = a_{33} = n_3 = 0$ since there are only two alleles; and there is only one way of arranging the gametic correlation table.

TABLE 3. GAMETIC CORRELATION FOR TWO ALLELES

	A_1	A_2	TOTAL
A_1	a	b	$a + b = n_1$
A_2	b	c	$b + c = n_2$
Total	$a + b$	$b + c$	N

The foregoing five methods, when applied to the two-allele ($k = 2$) case, yield the following estimates:

$$f = 1 - \frac{Nb}{(a+b)(b+c)} \tag{1'}$$

$$f = \frac{Na - (a+b)^2}{N(a+b) - (a+b)^2} \tag{2'}$$

$$f = \frac{ac - b^2}{(a+b)(b+c)} \tag{3'}$$

$$f^2 = \frac{1}{N} \cdot \frac{(ac - b^2)^2 N}{(a+b)^2(b+c)^2} \tag{4'}$$

$$f = \frac{a}{a+b} + \frac{c}{b+c} - 1 \tag{5'}$$

It may be easily verified that all of these five expressions are identical. In other words, the five methods described in the preceding sections will give the same results when there are only two alleles. These expressions are equivalent to one given by Haldane (1938) and by Li (1948) from a different consideration which is applicable only for the special case $k = 2$. Expression (4′) is

merely a restatement of the well known fact that $\chi^2/N = \phi^2$ is equal to the square of the correlation coefficient of any 2×2 table. This is most easily seen by comparing it to (3′). But the general expression (4) shows that Tschuprow's coefficient also reduces to the correlation coefficient for any $k \times k$ combination table of the type shown in Table 1.

7. MAXIMUM LIKELIHOOD

Application of the maximum likelihood method of estimation to the two-allele case is a straight forward process. As before, we use a, $2b$, c to denote the observed numbers of genotypes; and, to avoid subscripts, let p be the frequency of the allele A_1 and q be that of A_2 where $p + q = 1$. Then, the logarithmic likelihood function is, ignoring constant terms,

$$L = a \log [(1 - F)p^2 + Fp] + 2b \log [2(1 - F)pq] + c \log [(1 - F)q^2 + Fq]$$

Putting $\partial L/\partial p = 0$ and $\partial L/\partial F = 0$, these two equations upon simplification become

$$\left.\begin{aligned} \frac{a(2p + \theta)}{p(p + \theta)} + \frac{2b(1 - 2p)}{pq} - \frac{c(2q + \theta)}{q(q + \theta)} &= 0 \\ \frac{aq}{p + \theta} - 2b + \frac{cp}{q + \theta} &= 0 \end{aligned}\right\} \tag{6}$$

where $\theta = F/(1 - F)$. Eliminating their middle terms by multiplying the second equation of (6) by $(1 - 2p)/pq$ and then adding the two equations together, we obtain upon simplification the relation $aq/(p + \theta) = cp/(q + \theta)$. Hence, (6) may be written in the much more simplified form of two linear equations:

$$\frac{aq}{p + \theta} = b; \qquad \frac{cp}{q + \theta} = b. \tag{6′}$$

The simultaneous solution of these equations gives

$$p = (a + b)/N, \qquad \theta = (ac - b^2)/Nb, \tag{7}$$

the expression for θ here being equivalent to those for f listed in the last section (e.g. (3′)). Thus, for $k = 2$, the maximum likelihood estimate is the same as those given by our previous methods.

For $k \geq 3$, the authors have been unable to obtain explicit solutions for q_i and f from the k differential equations resulting from the partial differentiation of

$$L = \sum_i a_{ii} \log [(1 - F)q_i^2 + Fq_i] + 2 \sum_{i<j} a_{ij} \log (1 - F)q_i q_j .$$

It seems that the estimates of the gene frequencies are not given by the usual quantity n_i/N. Concerning this situation, Professor Wright made the following comments (personal communication):

"The inbreeding coefficient F, as a statistic descriptive of population structure, relates only to loci at which there are no significant selective differences among alleles. F should be substantially the same for all such loci whatever their gene frequencies. It is easy to construct a correlation matrix which is seriously inconsistent with the theoretical relations shown in your Table 1 and which could occur in a natural population only as a consequence of selection. In such a case the attempt to calculate F by the method of maximum likelihood might be expected to give estimates of the gene frequencies differing from those given by the marginal frequencies. The estimate of F from such loci as well as those modified estimates of gene frequencies would have little or no meaning."

In view of the obvious truth of the above comments, it would seem best to accept the observed gene frequencies ($q_i = n_i/N$) and estimate the value of F under this set of conditions in order to give F the biological meaning we attached to it. Hence, with given values of q_i, we only have to solve the equation $\partial L/\partial F = 0$, *i.e.*

$$\sum_i \frac{a_{ii}(1 - q_i)}{q_i + \theta} = 2 \sum_{i<j} a_{ij} \tag{8}$$

where $\theta = F/(1 - F)$ and $2\Sigma a_{ij}$ is the total number of heterozygotes in the sample. Note that when $k = 2$, it reduces to the second equation of (6). To solve (8) for θ, an initial trial value may be obtained from any of the five methods described in the foregoing sections and a more accurate solution for θ may then be obtained by iteration.

8. REDUCING THE NUMBER OF ALLELES

Instead of solving (8) as a whole, we may break it into component parts and just solve the following equation:

$$\frac{a_{ii}(1 - q_i)}{q_i + \theta} = \sum_j a_{ij}(i \neq j) = n_i - a_{ii} \tag{9}$$

That is, we set the fraction on the left side equal to half the number of heterozygotes containing the allele A_i. This equation is analogous to (6′) for the case of two alleles. Solving (9) for θ, we have, still taking $n_i = Nq_i$,

$$\theta = \frac{a_{ii} - n_i q_i}{n_i - a_{ii}} = \frac{a_{ii} - Nq_i^2}{Nq_i - a_{ii}}$$

or,

$$f = \frac{a_{ii} - Nq_i^2}{Nq_i(1 - q_i)} = \frac{Na_{ii} - n_i^2}{n_i(N - n_i)} \tag{10}$$

It should be noted that this approximation method is equivalent to pooling all the non-A_i alleles together as one allele, thus reducing the original $k \times k$ gametic correlation table into a 2×2 table involving only A_i and $\bar{A}_i$ as shown in Table 4 (the symbol $\bar{A}_i$ denotes non-A_i alleles; the bar on the top means "the negation of"). Applying the methods of estimating F for $k = 2$, we obtain the solution (10), which is the maximum likelihood estimate as far as the

TABLE 4. REDUCED 2×2 GAMETIC CORRELATION TABLE

	A_i	$\bar{A}_i$	TOTAL
A_i	a_{ii}	$n_i - a_{ii}$	n_i
$\bar{A}_i$	$n_i - a_{ii}$	$N - 2n_i + a_{ii}$	$N - n_i$
Total.............	n_i	$N - n_i$	N

TABLE 5. OBSERVED NUMBERS

	A_1	A_2	A_3	TOTAL	GENE FREQUENCY
A_1	28	17	15	60	$q_1 = 0.15$
A_2	17	94	49	160	$q_2 = 0.40$
A_3	15	49	116	180	$q_3 = 0.45$
Total............	60	160	180	400	1.00

TABLE 6. ESTIMATES OF F BY VARIOUS METHODS

METHOD OF ESTIMATION	VALUES OF f
(1) Total heterozygotes, H = .405; H_e = .615	0.3415
(2) Product-moment correlation	0.3823, .3231, .3274
(3) Gametic determinant, f^2 = .1206	.3474
(4) Chi-square, χ^2 = 98.74; f^2 = .1234	.3513
(5) Proportions of homozygous alleles	.3493
(8) Maximum likelihood, θ = .5232	.3435
(10) Reduction to two alleles	.3725, .3125, .3535
* Minimum Chi-square (Wright)	.3425

* See discussion.

data in Table 4 are concerned. Note that this pooling method is quite different from our first method of estimation (1). There are k ways of doing this kind of reduction. In practice, however, we may choose the allele with the highest frequency to be A_i and pool the remaining $k - 1$ alleles together. Similarly, we may reduce the k alleles to any number smaller than k. This procedure, though an approximate method, is perhaps advisable when some of the alleles have very low frequencies.

9. NUMERICAL EXAMPLE

We shall illustrate the various methods of estimation with the following hypothetical case involving 400 observed individuals (Table 5). The results of applying the various methods of estimation are listed in Table 6.

It will be noticed that the three estimates based upon the total proportion of heterozygotes, maximum likelihood and minimum Chi-square agree with each other very closely (.3415, .3435, .3425, respectively). The three different estimates based upon product-moment correlation as well as those by reducing the two alleles differ among themselves appreciably. All the other estimates are higher than .3435.

10. DISCUSSION

All of the methods of estimation described in this paper are simple enough, but, unfortunately, it appears difficult to assess the sampling variance of f for each case (particularly the determinant method). Hence, their relative efficiency cannot be compared at the present time. However, the significance of f can always be tested by Chi-square, as mentioned in Section 4.

After the value of f has been determined, a new Chi-square may be calculated using this value of f to see if the observed numbers are consistent with population Model II. For instance, method (1) gives $f = .3415$. Substituting this value together with the observed gene frequencies in II and comparing the estimated theoretical numbers thus obtained with those actually observed, we find $\chi^2 = 1.344$ with 2 degrees of freedom, corresponding to a random probability $P = 0.50$. Thus, the locus of this example yields an acceptable value of F. If P is still too small even when using this f, our Model II should be rejected. In the k allele case, the Chi-square has $[k(k-1)-2]/2$ degrees of freedom for this fitness test.

The minimum Chi-square estimate of F, though not discussed in the text, may be obtained by using trial values of f in II to determine sets of expected numbers. The minimum value of Chi-square is then calculated by comparing each of these sets with the observed numbers. The arithmetic procedure is quite analogous to that in solving the maximum likelihood estimate equation $\partial L/\partial F = 0$. The estimate by this method, $f = .3425$, as indicated in the last line of Table 6, was provided by Professor Wright.

An interesting and practical application of the knowledge about the value of F in a natural population should be discussed here. It may be shown that if a fraction ω of the individuals of a population practice self-fertilization while the remaining $1 - \omega$ mate at random in every generation, the population will soon reach an equilibrium condition with a value of

$$F = \frac{\omega}{2 - \omega}$$

(Haldane & Moshinsky, 1939, and others). This relation is entirely independent of the gene frequencies in the population. Plant breeders often wish to know the percentage of "natural self-fertilization" of a crop. For instance, it has been determined by various artificial means that in wheat the natural rate of selfing is about 99% with one percent natural "open cross". In cotton, on the other hand, there is mostly open crossing with only 10–20% selfing in natural conditions. Hence, if we choose a convenient "marker gene" without dominance which is more or less neutral to selection in cotton and maintain the cotton plot for a number of generations (not necessarily on the same field every year), the value of F estimated from the zygotic proportions of the plot will enable us to estimate the percentage of natural self-fertilization in cotton plants. For example, a value of $f = .081$ will indicate 15% natural self-fertilization in cotton. Further, once equilibrium is reached, it will remain that way from year to year. This will also enable us to study the variation of ω from year to year due to environmental factors as long as we maintain the cotton plot. This method of determining the percentage of natural selfing in plants may prove more accurate than the artificial devices employed by plant breeders as well as more economical.

SUMMARY

Seven methods of estimating the inbreeding coefficient have been described. They are based upon (1) total proportion of heterozygotes, (2) product-moment correlation between uniting gametes, (3) determinant of gametic correlation matrix, (4) value of Chi-square assuming panmixia in population, (5) sum of proportions of alleles in homozygous condition among their respective total frequencies, (8) maximum likelihood taking the observed gene frequencies as given, and (10) reduction of k alleles to two alleles. A numerical example for three alleles is given to illustrate the various methods. An eighth method, based upon minimum Chi-square, is also given in the numerical example in which it agrees with the maximum likelihood estimate very closely.

Sampling variances of the various estimates have not been assessed and therefore their relative efficiency cannot be compared at the present time. The test of significance of the value of the estimate (hypothesis $F = 0$), however, may be made by the ordinary Chi-square test against the model of panmixia.

When there are only two alleles, all of these methods are equivalent, yielding identical results.

A possible practical application in determining the percentage of self-fertilization in certain plants (such as cotton) under natural conditions has been discussed.

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The Genetics of Rheumatoid Arthritis

Analysis of 224 Families

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THE CAUSES of rheumatoid arthritis are not known. Many theories have been advanced and investigated but none of them adequately explain the clinical phenomena of this disease. It seems desirable, therefore, to investigate thoroughly all factors which seem to play a part in instituting the disease or in influencing its course. Heredity is one of these factors which seem to be of importance. The present study includes the analysis of 224 families of patients with rheumatoid arthritis from the standpoint of heredity.

Rheumatoid arthritis is a chronic systemic disease the most marked manifestation of which involves the joints. Though it may affect all ages, races and sexes, it usually begins insidiously in early adult life, it progresses irregularly with remissions and recurrences, leading eventually to crippling and deformity and sometimes producing complete and irreparable helplessness. Multiple joints are involved usually symmetrically but rarely if ever with the same rapidity or to the same degree. Fusiform swelling of fingers, wrists, knees and ankles are often seen, and there is often deformity, subluxation and ankylosis; subcutaneous nodules, tenovaginitis and muscular atrophy also occur. General health is impaired, and there is loss of weight, loss of strength, decline in vigor and decrease in physical activity. Radiographic examination shows demineralization of bones about affected joints, ulceration and destruction of joint surfaces, decrease in joint space because of loss of cartilage and, ultimately, bony ankylosis. There is rarely fever or leucocytosis, but the erythrocyte sedimentation rate is markedly increased. The patient's blood often shows ability to agglutinate streptococci in high dilution, but there is lack of antistreptolysin titer and antihyaluronidase, the last three characteristics being in marked contrast to the findings in acute rheumatic fever.

LITERATURE

No comprehensive coverage of the literature has been attempted. The data found were largely of the type which tells the number of patients reporting affected relatives without further effort to develop the data or to submit them to statistical analysis. The idea that rheumatoid arthritis runs in families or

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depends upon constitution or that the "virus must fall on fertile soil" emphasized particularly by Pemberton has been current for many years.

Those studies which do present pedigrees and attempt further analysis have assembled rheumatoid arthritis, rheumatic fever and osteoarthritis in the same tabulation and have treated the subject as though all rheumatic disease were related. This view is an old one. It is far from proven, however, and most modern investigators are strong in their feeling that these three diseases had best be handled separately. An extensive literature supports the view that susceptibility to rheumatic fever is inherited as an autosomal recessive trait, but the disease manifests itself only after sensitization following streptococcal infection. Osteoarthritis appears in many forms, each of which seems to have its own sex and age incidence, relation to hard work or trauma or to variation of anatomical development. Heberden's nodes, a form of osteoarthritis of the fingers, has been shown to be an autosomal, sex-influenced character, dominant in women and recessive in men. Osteoarthritis of the spine seems to follow hard work or injury. It is amazing to note how frequently acute rheumatic fever and rheumatoid arthritis appear together in different members of the same pedigree either in horizontal relationships in sibships or a vertical relationship of parent and child. No opinion can be offered as to whether or not there is a positive correlation between these diseases. It seems unlikely that such correlation will be found between rheumatoid arthritis and osteoarthritis.

Barter (1952) has presented a recent study on the familial incidence of rheumatoid arthritis and acute rheumatism, or rheumatic fever as we would call it, in 100 patients with rheumatoid arthritis. Of 538 members of families of patients, limited to brothers, sisters, fathers and mothers, 59 or 11 per cent were said to be affected. The incidence in the different grades of relationship varied considerably, being 5 per cent in fathers, 8 per cent in brothers, 13 per cent in mothers and 15.5 per cent in sisters. Of 543 members of the control families, 35 or 4.6 per cent were affected. The author concludes that an heredofamilial tendency toward the development of acute rheumatism or rheumatoid arthritis occurs in certain families. He discusses this constitutional tendency in relationship to Selye's "General Adaptation Syndrome" and Kendall's view that a hypersensitivity state may underlie rheumatoid arthritis. Regarding the former, certain individuals may have an hereditary weakness in their adaptation mechanism. Regarding the latter, it is suggested that certain individuals may have a constitutional tendency to react to the effects of an antigen-antibody reaction through the medium of the synovial membranes.

Short, et al. (1952), studied a group of 293 persons with rheumatoid arthritis and compared them with 293 controls. They found that 35 patients and 19 controls reported rheumatoid arthritis in the family without mentioning the relationship to the index cases, incidences of 11.9 and 5.1 per cent.

A similar study is reported by Davidson (1952) as an investigation instituted by the Scientific Advisory Committee of the Empire Rheumatism Council. This is based upon an extensive survey, including many factors, of 532 patients with rheumatoid arthritis and 532 controls. It was found that rheumatoid arthritis was reported in the study series in 7 per cent of fathers, 15 per cent of mothers, 3.8 per cent of 2151 brothers and sisters, compared to figures in the control series of 3 per cent of fathers, 9 per cent of mothers, and 1.8 per cent of 2143 brothers and sisters. The figures are statistically significant and lend support to the contention that a familial factor is of etiological importance. This figure suggests that rheumatoid arthritis is about 3 times as common in Great Britain as in the United States.

Edström (1941) reviewed in 1939 all the cases of chronic rheumatism admitted to the Lund Hospital from 1929 to 1933. His study is based on 504 cases of which 242 cases were rheumatic fever followed by chronic arthritis (Febris rheumatica c. arthritis chronica) and 262 cases of rheumatoid arthritis (Polyarthritis rheumatica chronica). The diagnoses of the last group seem to be readily understood. Some at least of the febrile arthritis seems also to fall in this group of rheumatoid arthritis, but a large proportion seem to have had acute rheumatic fever because they developed organic valvular heart disease. Edström includes seven pedigrees with data allowing recognition of rheumatoid arthritis. From these pedigrees 16 sibships were extracted. These included 81 sibs, which after correction for small family size on a 1:1 basis showed 33 affected compared to 45.3 expected affected. Penetrance for the entire group was 73 per cent. Forty-nine per cent of the families had only 1 affected individual, 32 per cent had 2 and 19 per cent had 3 affected. Strangely enough these figures are almost identical with those of the rheumatic fever group. Rheumatoid arthritis affected one or both members of 8 twin pairs. Of 4 sets of identical twins, 2 sets showed concordance for penetrance of 75 per cent; of 4 sets of fraternal twins, one set showed concordance. In the rheumatic fever group one set of identical twins showed both to be affected. Of 5 sets of fraternal twins, all showed only one member affected. One pedigree shows dentical twins with rheumatoid arthritis whose mother had rheumatoid arthritis, a brother and sister had rheumatic fever and one niece, daughter of an unaffected sister, had rheumatic fever. One twin married a man whose mother had rheumatoid arthritis. Seven of their eight children had rheumatic fever, two of them also developing rheumatoid arthritis. Seven children of the second twin were normal. Since rheumatic fever is inherited as a recessive, both twins seem to have been homozygous for the disease. One married a homozygote and had all children affected; the other married a normal and all children escaped.

Hangarter (1939) has published a book on heredity of acute and chronic rheumatism. He has included all rheumatic disease but he presents pedigrees

with sufficient detailed information to identify the chronic cases. Of 32 sibships 23 had one affected with what seems to be rheumatoid arthritis, 7 had 2 and 1 each had 3 and 4 affected. There were a total of 197 children with 43 affected with penetrance of 42.5 per cent.

Hölsti and Huuskonen (1938) reported a woman with rheumatoid arthritis who had 4 of 10 daughters and 1 of 3 sons affected with the disease.

Zellner (1930) reported 6 families with multiple involvement of rheumatic disease. According to the evidence presented, a mother and daughter, 2 sisters and a brother, and 2 sisters had rheumatoid arthritis.

Identical twins with concordant rheumatoid arthritis and cancer of the breast were described by Berglund (1940). Since this study was started, it has been discovered that 2 of our index cases are cousins, and that they had an affected aunt, the sister of their fathers. A proven instance has come to our attention of rheumatoid arthritis affecting a woman and her grandmother, the mother having died without arthritis of cancer at 28.

THE STUDY SERIES

The present study is based upon the family histories of 224 patients with rheumatoid arthritis. These were assembled as a group project by the physician authors from their private practices, the arthritic clinics and the wards of Cleveland City Hospital, St. Vincent's Charity Hospital, Mt. Sinai Hospital and Crile Veterans' Administration Hospital. Careful family histories were planned to reveal all the cases of rheumatoid arthritis which were known to have occurred among the parents, the siblings and the children of the index cases. The occurrence of rheumatoid arthritis among grandparents, uncles, aunts and cousins was recorded but cannot be considered to be complete. No predetermined combination of criteria was established to prove the diagnosis. This depended upon the judgment of the clinician. Many patients were seen by all three. Many patients had been under observation for years and had been subject to searching clinical examination and even autopsy. Other patients were accepted after a single examination. The index cases are considered to have been accurately chosen. It was not possible to examine all the secondary cases. Of 49 secondary cases reported as positive, 23 were dead when the study was made. Five were actually examined. The remaining 21 cases had to be accepted on the basis of history alone. In taking the family history, specific inquiry was made as to the age, state of health and age at death of each parent, sibling and child. Detailed questions were asked as to the presence or absence of arthritis, rheumatism or crippling disease. If any of the above were present, information was sought as to the age and circumstances of onset, duration and progression of disease, number and name of joints involved, the use of canes, crutches or wheel chairs and degree of disability which occurred. An attempt was always made to record the diagnosis given by the doctor.

Despite the fact that only 10 per cent of the secondary cases were examined, the diagnosis of the remaining cases was thought to be reasonably accurate. Very early and very mild cases were undoubtedly overlooked. It is believed, however, that a reasonably accurate account was obtained of all cases of well developed, deforming or disabling rheumatoid arthritis. Since the same technique was applied to the control series, it is believed that the findings of the study series and the control series are comparable.

Of the 224 families of patients with rheumatoid arthritis 47 reported a total of 57 secondary cases in their families. The affected relatives were reported to 49 be 8 fathers, 15 mothers, 5 brothers, 20 sisters, 1 son, 2 paternal aunts, 1 paternal grandfather, 1 paternal grandmother, 2 maternal grandmothers and 2 cousins. Affected relatives were reported in 47 of 224 families or 21 per cent. This rough tabulation simply indicates the familial nature of the disease, but it is of no use for statistical studies because information is not complete, and no evidence is presented as to the number of relatives which were considered.

In 224 index cases of rheumatoid arthritis, 93 patients were men, 131 patients were women. Two hundred twenty-four index cases, 447 parents, 849 siblings and 147 children were included to make a study group of 1667 individuals of whom 273 were affected. In these families, 49 secondary cases of rheumatoid arthritis were found among 1453 parents, siblings and children, an incidence of 3.1 per cent. This varied between the sexes, being 14 out of 704 or 1.9 per cent of the male relatives, and 35 out of 739 or 4.6 per cent among the female relatives. The incidence varied somewhat depending upon the relationship with the index case. Among parents, 23 of 447 or 4.5 per cent were affected. Among fathers this was 8 of 223 or 3.6 per cent; among mothers it was 15 of 224 or 6.7 per cent. It was 5 of 411 brothers or 1.2 per cent and 20 of 438 sisters or 4.6 per cent. Only 1 of 70 sons or 1.5 per cent were affected, but not one of 77 daughters were involved. The incidence among 1453 parents, siblings and children was 49 affected or 3.1 per cent.

These variations in incidence are due not only to difference in sex but also in part to age distribution. If computation is confined to relatives over the age of 50, we find the incidence of fathers to be 8 of 183 or 4.4 per cent, and of mothers to be 13 of 193 or 6.7 per cent; of brothers 4 of 192 or 2 per cent, and of sisters 14 of 203 or 6.9 per cent. There were only 4 children over the age of 50, none of whom were affected. Thus it is seen that rheumatoid arthritis was found in 3.1 per cent of 1453 relatives of rheumatoid arthritis, and 5 per cent of the 775 relatives over 50 years of age. The data are presented in detail in Table 1.

CONTROL SERIES

A control series was assembled from the family histories of 488 patients who did not have rheumatoid arthritis. These consisted of 260 families of pa-

tients seen in the office in consultation who were found to be free of rheumatoid arthritis. These included a large variety of diagnoses as well as no disease. To this group were added the data from 122 patients with Heberden's nodes, 59 patients with ankylosing spondylitis and 47 patients with gout. Data on the second group had been gathered for specific studies of these diseases. In most instances, the siblings were actually seen. Family histories were taken with the same care in the control group as had been used in the study group, and the results are comparable. The control series included 488 index cases and 2759 of their relatives, parents, siblings and children, of whom 16 were affected.

TABLE 1. INCIDENCE OF RHEUMATOID ARTHRITIS—FAMILY DATA

	TOTAL			MALE			FEMALE		
	No.	Affected	%	No.	Affected	%	No.	Affected	%
Study Series—224 Families									
Index Cases	224	224	100	93	93	100	131	131	100
Parents	447	23	4.5	223	8	3.6	224	15	6.7
Over 50	*376*	*21*	*5.6*	*183*	*8*	*4.4*	*193*	*13*	*6.7*
Siblings	849	25	2.8	411	5	1.2	438	20	4.6
Over 50	*395*	*18*	*4.5*	*192*	*4*	*2.0*	*203*	*14*	*6.9*
Children	147	1	0.7	70	1	1.5	77	0	0
Over 50	*4*	*0*	*0*	*4*	*0*	*0*	*0*	*0*	*0*
Total Relatives	1453	49	3.1	704	14	1.9	739	35	4.6
Over 50	*775*	*39*	*5.0*	*379*	*12*	*3.2*	*396*	*27*	*6.8*
Total Group	1667	273	15.8	797	107	13.4	870	166	18.3
Control Group—488 Families									
Total Relatives	2759	16	0.58	1348	7	0.52	1411	9	0.64
Over 50	*1530*	*14*	*0.9*	*721*	*5*	*0.69*	*809*	*9*	*1.1*

In analysing the 488 control families, the index cases are omitted because by definition they were all free of rheumatoid arthritis. Since each member of the family can be considered as an independent selection, the relationship to each other is of no significance; so the parents, siblings and children are assembled in one large group as a segment of the population selected at random. This population included 2759 individuals of whom 16 or 0.58 per cent were affected with rheumatoid arthritis. These included 7 of 1348 men, an incidence of 0.52 per cent affected, and 9 of 1411 women, an incidence of 0.64 per cent affected. If computation is limited to individuals over the age of 50, we find 5 of 721 or 0.69 per cent of men affected and 9 of 809 or 1.1 per cent of women affected, or a total of both sexes of 14 out of 1530, an incidence of 0.9 per cent.

Thus it is seen that rheumatoid arthritis affected all relatives of patients

with rheumatoid arthritis 5 times as frequently (3.1 per cent to 0.58 per cent) as it did the population in general, and in people over 50 years of age relatives were affected 6 times as frequently (5.8 per cent to 0.9 per cent) as the population in general. The study is made on 224 families of arthritis with 1667 relatives and 448 controls with 2759 relatives, a total of 4914 individuals of whom 289 had rheumatoid arthritis.

HEREDITY IN RHEUMATOID ARTHRITIS

If one assumes that rheumatoid arthritis is caused by a constellation of conditions to which the whole population is uniformly exposed and to which everyone is equally susceptible, then the multiple occurrence in sibships should follow the law of small independent probabilities, and thus conform to the Poisson distribution.

In the present study there are 203 sibships with 1 person affected, 17 sibships with 2 affected, 3 with 3 and 1 with 4 affected. For applying the Poisson

TABLE 2. TESTS OF POISSON DISTRIBUTION RHEUMATOID ARTHRITIS

NO. OF CASES PER FAMILY	NO. OF SIBSHIPS FOUND	EXPECTED NUMBER
0	12180	11937
1	203	240
1	17	2.4
3	3	0.016
4	1	0.00008

distribution, it is necessary to have an estimate of the number of sibships with none affected from the equivalent population. For this estimate it seems permissible to use the 488 sibships of the control series. The control series contained 16 individuals with rheumatoid arthritis. Eight of these were found as sibs of the index cases; 8 others were found among the parents. Since only sibs are admissible in the following computations, there are 8 affected sibs in 488 families or one affected in 60 families. Then a sample from the population which gives at random 203 sibships with one affected would give 60×203, or 12,180 sibships with none affected.

The comparison between these figures and the expected number of sibships calculated on the basis of the Poisson distribution may be seen in Table 2. Since the 1 per cent level of significance for 3 degrees of freedom gives chi square = 11.34, it can be seen from the table without further calculation that the series of multiple occurrences of rheumatoid arthritis observed in the present study does not by the longest chance conform to the law of small independent probabilities. The conclusion is unavoidable that the basic causal factor in rheumatoid arthritis is very probably genetic.

THE SEX RATIO

It is usually said that two times as many women as men get rheumatoid arthritis. This is borne out by certain aspects of the present data. Of the entire series there are 166 women and 123 men. As pointed out the large number of men is a result of the non-random sampling from hospital clinics and the admission of index cases from the Veterans' Hospital. There were 23 parents of the index cases affected of which 15 are mothers and 8 fathers, effectively a 2 to 1 ratio. Furthermore, excluding the index cases, there are 41 women and 16 men affected in the entire series, very close again to the usual ratio, 2.5 women to 1 man, and statistically significant since the deviation from a 1:1 ratio is over 3 times the standard error.

Twice as many women as men with rheumatoid arthritis is suggestive of a sex-linked dominant factor. But in a sex-linked dominant, a father transmits to all his daughters and to none of his sons. In this series with 8 fathers affected there were 5 with an affected son, which rules out the hypothesis of a sex-linked dominant factor.

The data on sibships may be used to test the homogeneity of the sexes independently of the selection of the material. It is found that sister-sister combinations occurred 20 times, brother-sister combinations were found 8 times and brother-brother pairs 3 times. Since the number of brother-sister (B) pairs is approximately twice the geometric mean of the number of sister-sister (A) and the brother-brother (C) pairs, it follows that these three numbers, giving the various sib-pair combinations, approximate a good fit to the binomial $(p + q)^2N$, where p and q are the observed proportions of females and males in all sib pairs.

$$p = \frac{2A + B}{2N} = \frac{40 + 8}{62} = 77 \text{ per cent}$$

$$q = \frac{B + 2C}{2N} = \frac{8 + 6}{62} = 23 \text{ per cent}$$

$$\chi^2 = 2.12 \qquad P \; ca \; 0.16$$

The chi-square test shows that it is reasonably probable that the sib pairs are homogeneous with respect to sex and confirms the conclusion from the analysis by inspection of the pedigrees that a sex-linked factor is not involved, although sex has an influence on the manifestation of the autosomal factor. This test shows a sex ratio of 3.35 women to 1 man.

IRREGULARITIES OF THE DATA

Variations in expressivity lead to irregularity in the data. Rheumatoid arthritis may begin as a violent, acute illness with prompt involvement of

many joints including swelling, pain and stiffness, leading in a few months to complete and irreparable helplessness. On the other hand, onset may be so mild and progress so slow as to make diagnosis difficult or impossible. No completely satisfactory specific tests of rheumatoid arthritis are available, and those which have limited value have never been widely used. Probably many affected people escape recognition.

One of the chief factors in causing the irregularity in the data on rheumatoid arthritis is the variable age of onset, which ranged from 13 to 71 years (Fig-

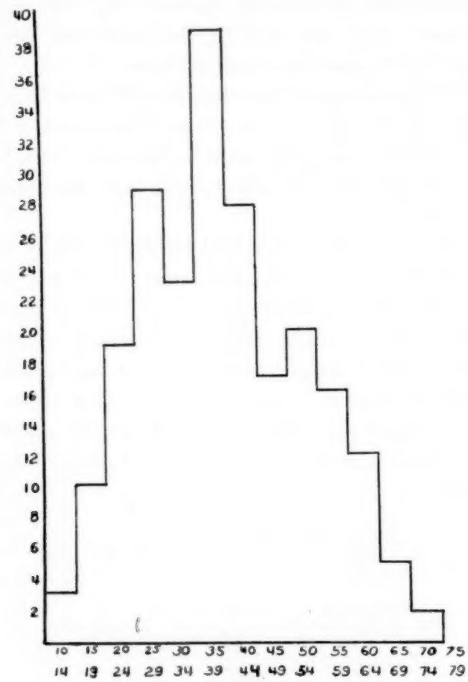

FIG. 1

ure 1). The average age of onset for 127 women was 38.7 ± 1.2 years with a standard deviation of 13.4 ± 0.84 years. For 96 men the corresponding figures are 40.3 ± 1.4 years and the standard deviation 13.5 ± 0.96 years. The difference in the average is 1.6 ± 1.8 years, clearly not a significant difference, although the view prevails that on the average women get rheumatoid arthritis somewhat earlier in life than men. For the two series combined, the average is 39.2 ± 0.9 years with a standard deviation of 13.5 ± 0.64 years.

Non hereditary influences which affect the fetus in utero have been recognized in the production of developmental anomalies, such as hare lip, cleft

palate and mongolian idiocy. These factors are not recognizable from the data at hand. There is no information about the maternal age at time of birth or of the comparative ages of onset of the affected sib pairs. Data is presented in Table 3 as to the birth order of the patient compared to family size. The birth order seemed to be of no significance. In the calculation the last class has been omitted because of the small numbers. The result shows X^2 (for 8 degrees of freedom) equals 5.557 which is P ca 0.70. There is no relationship between birth order and susceptibility to rheumatoid arthritis.

TABLE 3. RHEUMATOID ARTHRITIS

BIRTH ORDER OF PATIENT VERSUS FAMILY SIZE

FAMILY SIZE	BIRTH ORDER										TOTAL	EX-PECTED
	1	2	3	4	5	6	7	8	9	12		
1	18										18	
2	13	15									28	14
3	12	13	7								32	10.66
4	12	7	3	8							30	7.50
5	8	6	11	6	7						38	7.60
6	3	5	2	4	6	9					29	4.83
7	2	3	5	6	1	3	7				27	3.85
8	5	2	4	2	2	3	1	3			22	2.75
9	0	2	1	2	1	0	1	2	2		11	1.22
10	0	0	0	0	0	1	0	0	2		3	0.33
11	0	0	0	0	0	0	0	0	0		0	0.00
12	0	0	0	0	0	0	0	0	0	1	1	0.08
13	0	0	0	0	0	1	0	0	0	1	2	0.15
Total observed......	73	53	33	28	17	17	9	5	4	2	241	
Expected...........	71	53	39	28.3	20.8	13.2	8.4	4.5	1.8	1.5		

ANALYSIS AS A DOMINANT

In genetic analysis of pooled human material it is usually necessary to correct for small family size. This has been done in Table 4 according to the method of Hogben (1933) for both simple autosomal dominant on a 1:1 basis and as a simple autosomal recessive on a 3:1 basis. As will be seen, penetrance is 44 per cent. When correction is made for age, it is seen that after the age of 50, 278.3 are expected to be affected instead of 250 as found. This correction shows penetrance as a dominant of 49.5 per cent.

If rheumatoid arthritis is an autosomal dominant, and if there were nothing irregular in its inheritance, then at least one parent should be affected. Of the 224 index cases there were 23 with 1 parent affected. When these 23 sibships are pooled and correction is made for small family size, on the basis of 1:1 ratio, it is found that 28 are affected and 55 expected affected for penetrance

of nearly 51 per cent. Of the remaining 201 index cases neither parent is affected, but, on the assumption of a dominant, one parent at least should be heterozygous for the dominant factor, and so again a 1:1 ratio is expected. This showed 222 affected compared to 506 expected for 44 per cent penetrance. Since 23 parents out of 224 expected have rheumatoid arthritis, there is among the parents of the index cases a penetrance of about 10 per cent. This low penetrance seems clearly to be the result of low expressivity, resulting in some of the parents having had a mild or an unrecognized case of the disease or having died before the disease developed.

TABLE 4.* CORRECTION FOR SMALL FAMILY SIZE
Comparison of Affected Compared to Expected Affected Siblings

SIZE OF FAMILY	NO. OF FAMILIES	NO. OF SIBS	AFFECTED SIBS	SIMPLE AUTOSOMAL DOMINANT (1:1) RATIO		RECESSIVE (3:1) RATIO	
				Factor	Expected affected	Factor	Expected affected
1	16	16	16	1.	16.	1.	16.
2	29	58	31	1.333	38.657	1.1428	33.1412
3	30	90	30	1.714	51.420	1.2970	38.910
4	38	152	40	2.134	81.092	1.4628	55.5864
5	32	160	34	2.581	82.592	1.6389	52.4448
6	28	168	33	3.048	85.344	1.8248	51.0944
7	21	147	28	3.532	74.172	2.0196	42.4116
8	19	152	26	4.016	76.304	2.2225	42.2275
9	4	36	5	4.508	18.032	2.4321	9.7284
10	5	50	5	5.	25.	2.649	13.245
12	1	12	1	6.	6.	3.098	3.098
13	1	13	1	6.5	6.5	3.329	3.329
Total..........	224	1054	250		561.113		361.2163
Correction for age. Number expected affected after 50 years: 278.3				Penetrance—44.6% Penetrance—49.5%		Penetrance—69.2% Penetrance—77%	

Because of the known difference in sex incidence in rheumatoid arthritis, penetrance was computed for each sex separately. This was done by considering all the sibs of the same sex as the index case and disregarding those sibs of the other sex. This method eliminates many unaffected sibs. The tables are not given, but the final summary shows that 99 of 243 males were affected compared to 158 expected, for a penetrance of 63 per cent. There were 155 of 393 females affected compared to 232.5 expected, for a penetrance of 66 per cent. In the two series there was consequently a total of 628 individuals compared to the 1054 of the original table. Increased penetrance in this instance was due to elimination of 426 unaffected sibs from the computation. These are surprising results on penetrance in view of the greater incidence of rheumatoid arthritis in the female sex which are not readily explained.

ANALYSIS AS A RECESSIVE

If we entertain the assumption that rheumatoid arthritis is an autosomal recessive, Table 4 shows 361 expected affected on a 3:1 basis compared to 250 found affected, a penetrance of 69.2 per cent. When correction is made for age, there are 278 finally affected compared to 356 expected for penetrance of 77 per cent. In 23 families one parent is affected or homozygous; the other parent is assumed to be heterozygous. Inheritance will be on a 1:1 basis, and after correcting for small family size, 51 per cent penetrance is found. Neither of the parents in 201 remaining families are affected, so 3:1 inheritance is expected. Thus it is found that 380 are expected affected compared to 250 found for penetrance of 66 per cent.

GENE FREQUENCY

The data are irregular in the sense that they do not conform to any simple Mendelian mechanism. In the early days of applying Mendelian ratios to human data, the irregularities in the data not infrequently led to the postulation of complex genotypes which failed to be convincing. In the present series there are 23 cases with one parent affected, in the other 201 neither parent shows the trait. This is the equivalent of skipping a generation in the more extensive pedigrees. This is suggestive of a simple recessive, but it is also recognized that a dominant with diminished penetrance resembles a recessive in many pedigrees, depending upon the degree of penetrance. Perhaps most genes for defective traits are recessive to the normal, but in many cases, owing to the system of outbreeding in human society, they are for the most part kept in a heterozygous state. Consequently, the results of cousin marriages are especially important in deciding between a dominant, with diminished penetrance, and a recessive. In the present series no cousin marriages were found, but Wittinghill and Hendricks (1951) in a brief report of an extensive pedigree which included ten cousin marriages ruled out recessive inheritance. This strengthens the probability that rheumatoid arthritis is an autosomal dominant.

From the analyses above there is no way to be sure directly from the numerical tests of the data whether rheumatoid arthritis is an autosomal dominant with about 50 per cent penetrance or an autosomal recessive with a higher penetrance in the neighborhood of about 70 per cent. The conclusion from such tests, however, needs to be reasonably consistent with the gene frequency in the population which supplied the sibships. Since the attempt to estimate the penetrance in males and females separately revealed no essential difference, it seems best to take an overall figure of 50 per cent for the case of a dominant and a round figure of 70 per cent if rheumatoid arthritis is a recessive. Another figure which is needed for the calculation of the gene

frequency is an estimate of the incidence of rheumatoid arthritis in the population of Northern Ohio, which supplied the data for the study series. The control series included a total of 2759 individuals of whom 16 or 0.58 per cent were affected with rheumatoid arthritis. For the United States with 156,000,000 people, of whom 60 per cent are above 20 years, it turns out that there should be 543,000 persons with rheumatoid arthritis. Since these include only obvious, undoubted and advanced cases, it is seen that this is quite compatible with

TABLE 5. RHEUMATOID ARTHRITIS

GENE FREQUENCY AS DOMINANT

	d 0.006	r 0.994
d 0.006	dd 0.000036	dr 0.00596
r 0.994	dr 0.00596	rr 0.9884

50% Penetrance
dd and dr are affected. rr are normal.
d = 0.006 r = 0.994

TABLE 6. RHEUMATOID ARTHRITIS

MATING AS DOMINANT

		Constitution of the Father		
		dd 0.000036	dr 0.0119	rr 0.9884
Constitution of the Mother	dd 0.000036	dd × dd 13×10^{-10}	dd × dr 43×10^{-8}	dd × rr 36×10^{-6}
	dr 0.0119	dd × dr 43×10^{-8}	dr × dr 0.00014	dr × rr 0.0118
	rr 0.9884	dd × rr 36×10^{-6}	dr × rr 0.0118	rr × rr 0.9769

dr × rr should contribute 99.88 per cent of the affected families or 223.7 out of 224 of this series.
rr × rr are matings with normal offspring only.

the estimate of the Arthritis and Rheumatism Foundation of 700,000 cases of rheumatoid arthritis in the United States.

Since the estimate of the penetrance is 50 per cent, the gene frequency of individuals with a genetic constitution for rheumatoid arthritis is twice this or 0.0116. With random mating of a population in genetic equilibrium the homozygous dominants, the heterozygotes and homozygous recessives are present in the relative frequencies $d^2 + 2dr + r^2 = 1$ where d is the frequency of the factor for rheumatoid arthritis, r is the frequency of the normal recessive allele, and $d + r = 1$. Consequently the frequency of d is 0.006 and the value

for r is 0.994. The frequency of those homozygous for the dominant factor for rheumatoid arthritis is 36 in a million and the heterozygotes are nearly 12 per thousand (Table 5). It may be seen in Table 6, that practically all matings expected are rr × rr or dr × rr, and that those including a person dd in constitution are exceedingly rare.

TABLE 7. RHEUMATOID ARTHRITIS

GENE FREQUENCY AS RECESSIVE

	d 0.909	r 0.091
d 0.909	dd 0.8263	dr 0.0827
r 0.091	dr 0.0827	rr 0.0083

70% Penetrance

rr are affected. dr and dd are phenotypically normal.

d = 0.909 r = 0.091

TABLE 8. RHEUMATOID ARTHRITIS

Mating as Recessive

		Constitution of the Father		
		dd 0.8263	dr 0.1654	rr 0.0083
Constitution of the Mother	dd 0.8263	dd × dd 0.6828	dd × dr 0.1367	dd × rr 0.0069
	dr 0.1654	dd × dr 0.1367	dr × dr 0.0274 177	dr × rr 0.0014 22
	rr 0.0083	dd × rr 0.0069	dr × rr 0.0014 22	rr × rr 0.00007 3

rr constitution is the only one genotypically susceptible. They are possible only in the matings of the lower right hand corner.

The second number gives the distribution expected of 224 families although individual families cannot be identified.

On the other hand, if rheumatoid arthritis is a recessive with 70 per cent penetrance, then the frequency of genotypes for the disease in the population is 0.0083. Again, assuming random mating and genetic equilibrium, the value of r is 0.091 and for d the frequency is 0.909 (Table 7). The frequency of heterozygote is therefore 2dr or 0.1654. About 1 in every 6 of the population is carrying the recessive factor for rheumatoid arthritis. The expected frequencies of the various types of matings are given in Table 8.

Another minor point, which may be worth mentioning, is that the best known recessives in human genetics, such as albinism, blue eyes, phenylkatonuria, and alkaptonuria, are remarkably uniform in their manifestation, in contrast to the great variability of many of the undoubted dominants. From this analysis and from the previous considerations, it seems more plausible that rheumatoid arthritis is an autosomal dominant with about 50 per cent penetrance.

DISCUSSION

It seems desirable to give some consideration to the nature of rheumatoid arthritis. Many theories of etiology have been advanced and have successively held ascendancy for varying periods of time, only to be supplanted later as the mode or as scientific discovery seemed to dictate. This is not the place for a full discussion on the subject aside from presenting some of the facts revealed in a recent comprehensive, cooperative survey conducted by the Scientific Advisory Committee of the Empire Rheumatism Council and presented in 1950 (Lewis-Faning) as a supplement to the "Annals of Rheumatic Disease." This study depends upon data assembled from numerous arthritis clinics and research centers in Great Britain. Five hundred thirty-two patients with rheumatoid arthritis of less than 5 years duration were matched with the same number of people of the same age, sex, marital experience and no arthritis. Detailed histories revealed a strikingly similar experience in both groups. The sex ratio of the patients was 100 men to 132 women. The mean age of onset was 42 for men and 41 years for women. These figures compare with 40 and 39 years in the present series. Forty-three specific diseases were listed in the questionnaire, but no statistical difference was found between the two groups. The same result was found concerning psychological precipitating factors which were found in 39 per cent of both groups.

Infection noted within 3 months of onset were found in 19 per cent of patients compared to 11 per cent of controls. While this is a statistically significant difference, it was pointed out that patients are more likely to reveal these facts than are the controls. Besides this, infections were not noted before onset in 80 per cent of patients. Allergic diseases, endocrine diseases, focal sepsis, pregnancy and menstrual disorders and occupations did not seem to be significantly different.

Certain clinical features of rheumatoid arthritis were confirmed by this study. These included abnormalities of the peripheral circulation, sweaty hands, sweaty feet and cold fingers, found in 43, 36 and 15 per cent of patients compared to 6, 3 and 5 per cent of controls. Prodromal symptoms such as fatigue and loss of weight were noted, and it was confirmed that small joints are usually affected first, that involvement tends to be symmetrical and that exposure to cold and wet adversely affect arthritis. The most significant find-

ing of the study was that the incidence of involvement in relatives was about twice as great in patients as in the controls.

This extensive study revealed no hint as to the extrinsic factors which play a part in the causation of rheumatoid arthritis, but suggest the importance of constitutional factors as they are determined by heredity.

An explanation for some of the phenomena of rheumatoid arthritis can be sought in the fields of experimental biology and heredity. The data clearly indicate that the main factor is genetic and autosomal. To proceed with the analysis, it is necessary to make the assumption that the genetic factor is the same in all sibships. To completely justify this assumption the data would have to include extensive linkage studies, which are still hopelessly inadequate in human genetic analysis. The assumption implies that the irregularity in the data is not the result of several different major factors for rheumatoid arthritis. In the present state of knowledge nothing can be said of multiple alleles at the main locus.

There is a bare possibility that rheumatoid arthritis may be dominant in some families, recessive in others. If a person were heterozygous for the dominant gene and the modifying factors suppressed its effect, the gene would have a chance to spread through the population, particularly if the reproductive fitness of such people were greater than their sibs with dominant rheumatoid arthritis. Depending on the number and strength of the genetic modifiers, it could come about that the patient would need to be homozygous for the main gene for rheumatoid arthritis to manifest itself. This is merely conjectural in the case of rheumatoid arthritis, although the mechanism is known, from experimental genetics, in which a gene is dominant with one set of modifying factors and recessive in the presence of other modifying factors. This situation is known to prevail in baldness in women (Osborn, 1916), Heberden's nodes in men (Stecher, et al., 1944), coat color in cattle and horns in sheep (Snyder, 1946). In certain lines of inbred guinea pigs, Wright (1934) found that 2 times as many females as males are otocephalic monsters.

THE CAUSES OF RHEUMATOID ARTHRITIS

The primary cause of rheumatoid arthritis is not known. So many different and contradictory theories have been advanced that the fact itself requires an explanation. From experimental zoology, phenomena are known in which a wide variety of physical and chemical agents can trip an intrinsic mechanism, which is the sine qua non for some vital process to occur. The outstanding examples of this are the many physical and chemical agents which have been successfully employed in studies on artificial parthenogenesis and the many factors which are known to successfully produce the organizer effect in studies on Amphibian embryonic development. It seems that a somewhat similar situation exists in regard to rheumatoid arthritis. Although some data show

that an infectious agent has been found in about 30 per cent of the cases, no one has ever demonstrated a specific pathogenic agent for the disease. In a similar way, although about 30 per cent of the patients show an abnormal basal metabolic rate, the other patients are normal in this respect. Emotional stress, altered Ca and P metabolism, hypochlorhydria and other factors have been suggested as the etiological factor in rheumatoid arthritis, but without any convincing demonstration. It is hardly an exaggeration to say that whenever an internal physiological or an external condition of stress has been found between the rheumatoid arthritis patient and the normal, someone has suggested the condition as the cause of rheumatoid arthritis. This is an instance of the common fallacy that gives up the search for the factor that is common to all cases of rheumatoid arthritis and to find over what physiological pathway the common factor acts to produce its effects.

These factors which have been mentioned as well as others not listed as among the suggested causes of rheumatoid arthritis may be regarded as contributory factors which tip the balance or bring about a proper physiological state for the onset of rheumatoid arthritis. And some, no doubt, act to affect the progress of the disease, to make it more devastating in some cases or to ameliorate the effect of the disease in others.

The pooled data are analyzed above both from the standpoint of an autosomal dominant and an autosomal recessive. But first it is important to discuss the irregularities in the data. In almost all, if not actually in all, cases of extensive data on human hereditary traits, irregularities appear. As pointed out, the irregularities in the early days, on the tacit assumption that penetrance was complete, often led to the postulation of complex genotypes which were unconvincing. When the irregularity in the data was slight, the few exceptional cases were usually explained away on the basis that the legal parentage did not coincide with the biological parentage, owing either to illegitimacy, to concealed adoption or the unrecognized switching of infants.

Irregularity in the data due to variable age of onset has been presented above. The age of onset refers to the effective or critical time in the life cycle when the phenotypic trait becomes manifest. Obviously the great variability in the age of onset is not the result of any lack of precision in biological processes, but instead is an indication of considerable complexity in the internal and external subsidiary causal factors. When the genetic factors and the external factors are constant from individual to individual, then the critical period for the population may be greatly restricted. For example, in certain highly inbred lines of mice which presumably have an extreme degree of homozygosis, Dunn (1940) and his collaborators have been able to show that a lethal effect in a certain tailless mouse stock is produced at $10\frac{3}{4}$ days in all mice with the genetic constitution for the lethal action. In other words, the time for the effective action of the genes, or the age of onset, is greatly restricted and is essentially the same for all the mice of the stock with the

appropriate genetic constitution, and consequently the critical period is very short, and there is 100 per cent penetrance.

But in several closely inbred lines of guinea pigs with polydactyly and presumably also each with the same high degree of homozygosis, since they were inbred by brother-sister mating since 1906, Wright (1934) found that the penetrance differed and varied in each line predominantly with the age of the mother, but also there was a seasonal variation. It is of especial interest and importance for human genetics that Wright's analysis showed that the several inbred lines which differed in the degree of penetrance with age of the mother differed in several genetic modifiers which also affected the degree of penetrance.

It seems in this case that the critical period for the determination of polydactyly was also greatly restricted in duration, and the inbred lines differed in the degree of penetrance at different ages of the mother because of the subsidiary genetic modifiers in which the several lines differed.

In these different strains of guinea pigs, the degree of penetrance decreased with increasing age of the mother, which is in contrast to the classic human case of Mongolism in which the penetrance increases with the age of the mother toward the end of the reproductive period (Penrose, 1938).

The instances mentioned concern traits which come to expression during the gestation period, and so are present at the time of birth. For hereditary characters which become manifest after birth or during adult life there is, at least so far as human data go, a great length to the critical period in the life cycle when the trait may manifest itself in that fraction of the population which has a genetic constitution for the trait. For example, in the case of Heberden's nodes (Stecher, et al , 1944), the conclusion drawn from the data was that the population had passed the effective period at an advanced age, about the ninth decade, and penetrance was complete. A similar phenomena is observed in the case of Huntington's chorea, and in Leber's optic atrophy (Bell, 1935). In the case of rheumatoid arthritis it was demonstrated that at an advanced age, the penetrance is little more than 50 per cent even though the population by and large has passed through the effective period.

The traits mentioned above from the field of experimental genetics which showed an effect of the age of the mother are characters which come to expression during the period of gestation. Although it is not impossible, yet it seems improbable that a difference in the age of the mother at the time of gestation would cause a difference in the development of a trait which comes to expression much later in adult life. The data at present are not available to test whether there is any causal relation between age of mother at gestation and the time of onset for rheumatoid arthritis in the progeny, and this perhaps holds for any other adult human hereditary trait. The same conclusion applies to the seasonal effect, which Wright found in the polydactylous guinea pigs mentioned above. But it is clear that the only way in which the matter can

be adequately tested would be for such data to be included in pedigrees collected in the future.

The conclusion that many individuals in early and later old age have a genetic constitution for rheumatoid arthritis but are not recorded as arthritics requires some special comment. The curve for the age of onset mentioned above is made up of two components. The one is for the individual and embraces the time from the very first recognizable beginnings of rheumatoid arthritis until the full development of the disease. This is obviously much longer than the restricted time for characters which develop during the embryonic or fetal period as in the tailless lethal mice mentioned above. Since this time for the development of rheumatoid arthritis in the life cycle varies from individual to individual, the second component is made up of the critical period for the population which extends almost throughout the entire adult life and according to the data from the present series begins at age 13. The dissection of such a curve was made for the temperature effective period for the reduction of certain bristles in Drosophila melanogaster by Child (1935), who clearly pointed out the compound nature of such curves. In the case of D. melanogaster, since the data were collected from adults, the embryonic curve could be inferred only indirectly. But in the case of hereditary human traits which become manifest in the adult, such curves can be dissected on the basis of direct observations, but the data on rheumatoid arthritis are not adequate for the task. One thing, however, is clear: in many individuals rheumatoid arthritis has an insidious onset and may not come to the attention of the clinician sometimes for years. This, of course, extends the age of onset at the upper limits of the curve.

An illuminating example in some respects is supplied by Gordon's (1951) work on the experimental genetics of platyfish and swordtails. For example, in crossing geographical races of platyfish, he found in F_1 a diminished penetrance in the development of melanomas, which was dependent upon genetic modifiers in which the two geographical races differed, similar to the case of polydactylous guinea pigs of Wright mentioned above. But it is also clear in the results from Gordon's fish crosses that the major gene for macromelanophores was the sine qua non for the development of the melanoma. Gordon emphasizes that the diminished penetrance and lowered expressivity was dependent upon the subsidiary genetic modifiers in which the races differed. In at least one cross Gordon found a diminished penetrance accompanied by a heightened expressivity. This may also be the case sometimes with rheumatoid arthritis in those families where a son or daughter develops a worse case of arthritis than a parent. In his discussion Gordon emphasized what Little (1947) pointed out in a discussion of the incidence of tumors in hybrid mice that the experimental study of the genetics of hybrids is of special importance in the study of irregular human traits. And since in America the "melting pot" is an extraordinary mixture of biological types from diverse geographical

areas, the degree of heterozygosis is an important factor in the production of irregularities in human genetic data. Moreover, Heston (1951) in a recent discussion of the genetics of neoplasia in mice says, "... the development of mammary tumors in mice is influenced by many extrinsic and intrinsic (genetic and non-genetic) factors whose effects are cumulative in increasing the probability that the tumors will occur."

The mild and quiet cases which may never come to the attention of the physician, the cases with sub-clinical manifestations or in genetic terms, with low expressivity, affect the estimate of the expressivity and consequently the degree of penetrance. The differences in age of onset, in the time for definitive development in the individual, the low expressivity and the diminished penetrance in rheumatoid arthritis and the presence or absence of external conditions of stress, are all perhaps an expression of subsidiary genetic modifiers.

The analytic results from the field of experimental vertebrate genetics allow the conclusion that irregularities in human data may be caused by diverse internal and external factors. Age of mother, seasonal effects, secondary genetic modifiers and factors still unknown may all act to produce variability in age of onset, diminished penetrance and altered expressivity. The irregularities in the data on rheumatoid arthritis apparently involve some or all of these factors which have been demonstrated in experimental genetics.

SUMMARY

This study is based on pedigrees of 224 patients with rheumatoid arthritis, including 1677 persons, which are compared with pedigrees of 488 controls, including 2759 persons. Of relatives of rheumatoid arthritis patients, 3.1 per cent of all relatives and 5 per cent of relatives over 50 years of age had rheumatoid arthritis, compared to 0.58 per cent of all relatives and 0.9 per cent of relatives over 50 years of age in the control group. That heredity affects rheumatoid arthritis is indicated by the lack of agreement with the Poisson distribution of multiple cases.

The data are extremely irregular due in part to irregular penetrance and a number of exogenous influences which affect expressivity. When correction is made for small family size, penetrance is found to be about 50 per cent as a dominant and 70 per cent as a recessive. Gene frequency analysis as a dominant shows 6 genes per thousand for the trait, and matings at random will provide 36 in a million as homozygous for the trait, 12 per thousand as heterozygous susceptible and the rest homozygous normals. If rheumatoid arthritis is assumed to be a recessive with 70 per cent penetrance, 9 per cent of genes are recessive for the trait, and mating at random provides 8 per thousand homozygous susceptible.

Intrinsic factors are proving to be of increased importance in the etiology of rheumatoid arthritis. Explanations of the phenomena of rheumatoid arthritis are sought in the fields of experimental biology and heredity. Variations in

penetrance and irregularities of expressivity can be explained by diverse internal and external factors acting as secondary gene modifiers.

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Multiple Cutaneous and Subcutaneous Lesions Occurring Simultaneously with Hereditary Polyposis and Osteomatosis[1]

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THREE widely different manifestations of abnormal growth were observed in the same six members of a family group consisting of 51 individuals. Forty-four members were found to be free from all three abnormalities. One child had one of the three types of abnormal growth. The kindred first had been encountered in an investigation (Gardner, 1951) of the incidence of intestinal polyposis.

All fifty-one living members were examined by appropriate clinical methods for intestinal polyposis. In the course of these examinations "surface tumors" were also observed. These were of two types—hard and soft. Family members referred to the hard lumps as "bone tumors" in contrast to the "soft tumors" which were confined to the cutaneous and subcutaneous tissue. The "bone tumors" were investigated (Gardner and Plenk, 1952) by means of roentgenological examinations of the skull and forearms in all members of the group and the entire skeleton when warranted. Pathological studies were made from four individuals and the diagnosis of osteomatosis was established. The same six patients with intestinal polyps also had multiple osteomas. None of those free from intestinal polyps had osteomas. The pattern of inheritance (Gardner, 1951; Gardner and Plenk, 1952) for both the intestinal polyps and the osteomas was interpreted as that of a dominant gene. Either a single pleiotropic gene responsible for both manifestations, or two closely linked genes would account for the data. The nature, incidence and mode of inheritance of the "soft tumors" will be considered in this paper.

RESULTS OF EXAMINATIONS FOR "SOFT TUMORS"

Three kinds of "soft tumors" were found to be prevalent in the group. These were identified by microscopic examination as epidermoid cysts, fibromas and ill-defined masses of connective tissue. More than one type occurred in the same individuals. Some sibs had cutaneous and subcutaneous lesions while others living in the same home had none. In one family including two children,

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the father and younger daughter had multiple epidermoid cysts while the other daughter was free from such lesions. In another family the father and two of the three children had "soft tumors" while the third who was intermediate in age had none. It is probable, although demonstrated pathologically in only three, that all six individuals had connective tissue masses or fibromas.

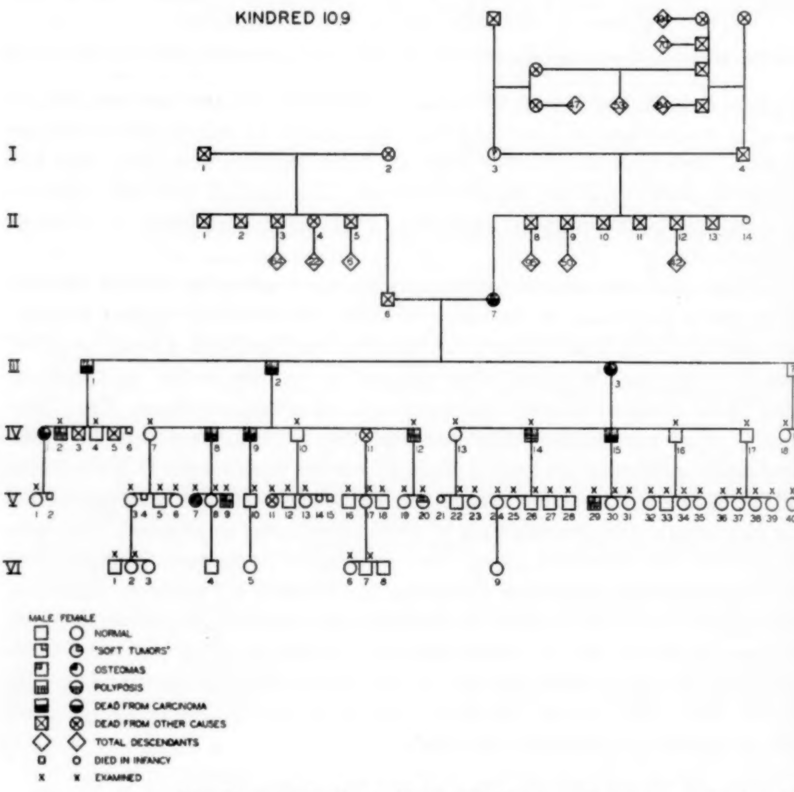

FIG. 1. Pedigree of family group showing incidence of "soft tumors," osteomas, and polyposis

The family group is represented diagrammatically in figure 1. Positive results of previous examinations for intestinal polyposis and osteomatosis as well as those for "soft tumors" are indicated on the chart. Laboratory examinations including hematocrit, stool guaiac tests, blood analysis for calcium, phosphorus, total serum protein, albumin, globulin, and alkaline phosphatase were conducted in four patients with growth abnormalities. Six individuals (IV-2, IV-12, IV-14, V-7, V-9, and V-29) were found to have multiple polyps of the colon and multiple osteomas in the skull bones. These same six patients were

observed to have multiple cutaneous and subcutaneous lesions. The case results and pertinent histories are summarized as follows:

When examined, IV-2, age 45, had on his back three lesions varying from 3 to 6 cm. in diameter. One removed from the lower mid region of the back for pathological study is illustrated in figure 2. This patient had several similar lumps on his arms, legs and head. One "soft tumor" 6 cm. in diameter was observed in the inguinal area. The patient remembered conspicuous soft lumps on different parts of his body continuously since he was about 14 years of age. Neither IV-2 nor his close relatives could be sure whether or not the growths were present in earlier childhood.

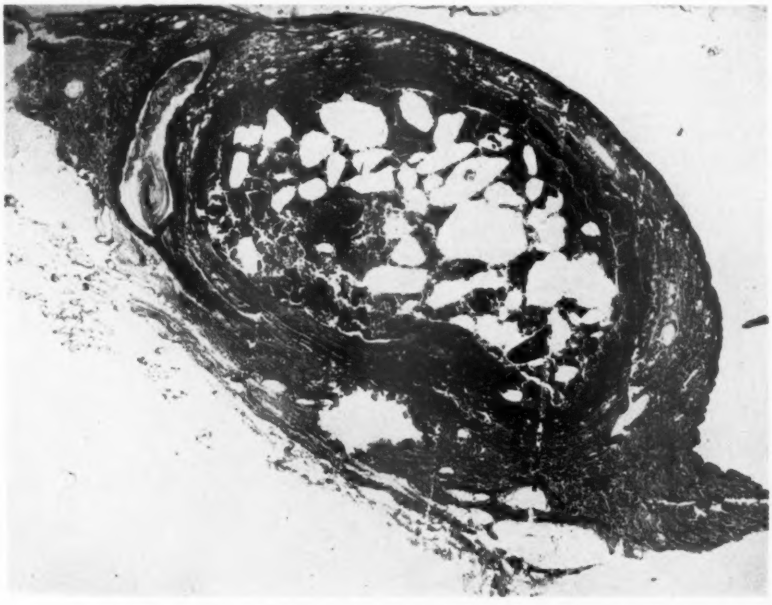

FIG. 2. Cross section of lesion removed from IV-2 in lower mid region of back

At the time of the examination IV-12, age 32, had four conspicuous lesions, on his back and one on the right shoulder (Fig. 3). Twenty-six "soft tumors," some firm and fibrous, were counted on his body. Five were resected for study and identified as epidermoid cysts. Numerous lesions, mostly epidermoid cysts but some fibrous masses, had been removed periodically over a period of years by the family physician. Seventeen had been taken from this patient at one time. Two lesions, removed from the head some years before the present examination, were described by the surgeon as leathery and fibrous in nature. They had been called fibromas although no pathological study was made.

Numerous "wens" had been observed on the body of IV-12 by his close associates from early childhood. His daughter (V-20), age 6, also had several cysts on her face and body which had persisted since early childhood. One was removed from the face of V-20 and identified as an epidermoid cyst.

IV-14, age 43, had several hard apparently fibrous masses on his body. Four were removed previously from different parts of the body including the area behind the ear, the navel, the lateral aspect of the thigh and the interscapular area. All of those removed were described as cysts. One measuring 1 cm. in

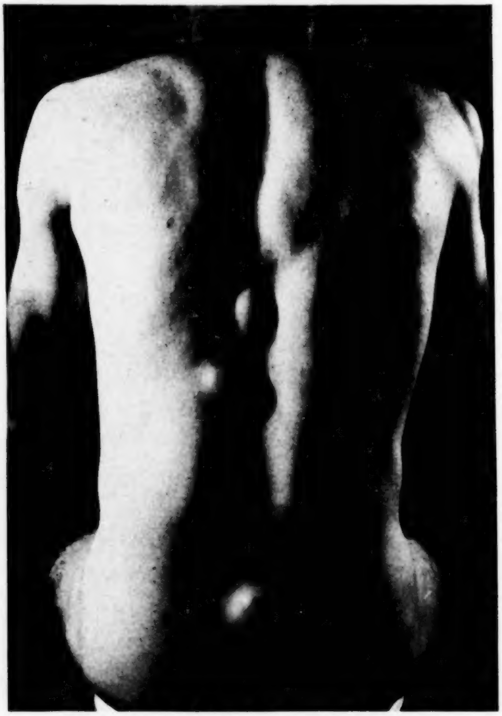

FIG. 3. Back of IV-12 showing epidermoid cysts

diameter was observed on the left eye lid at the time of the examination. In connection with a surgical procedure in 1927 for the removal of an osteoma in the frontal bone, a thick, fibrous mass was taken from the surface of the forehead. Soft irregularities were observed by IV-14 and his relatives on various parts of his body since his early youth.

When examined, V-7, age 20, had two hard fibrous lesions on her scalp and one on her forearm. A cyst had been previously removed from the side of her head. The lesion on her forearm was biopsied and identified as collagenous

and fatty tissue. The tissue was similar to that diagnosed as "fibroma" in other patients but a capsule was not present. The younger brother (V-9), age 14, of V-7 had seven firm subcutaneous masses on his head and body at the time of the examination. Most of these were on the scalp. They varied from 1 to 3 cm. in diameter. One was located on top of the left shoulder. Another was on the lateral aspect of the left forearm. A firm mass was located behind the right ear (Fig. 4). This was removed for microscopic study and identified as fibrous connective tissue, not encapsulated. The specimen measuring 3.5 x 2.4 x 1.2 cm. consisted of a leathery, almond-shaped mass of firm pearly grey tissue. The cut surface revealed slightly whorled fasciculated tissue which was

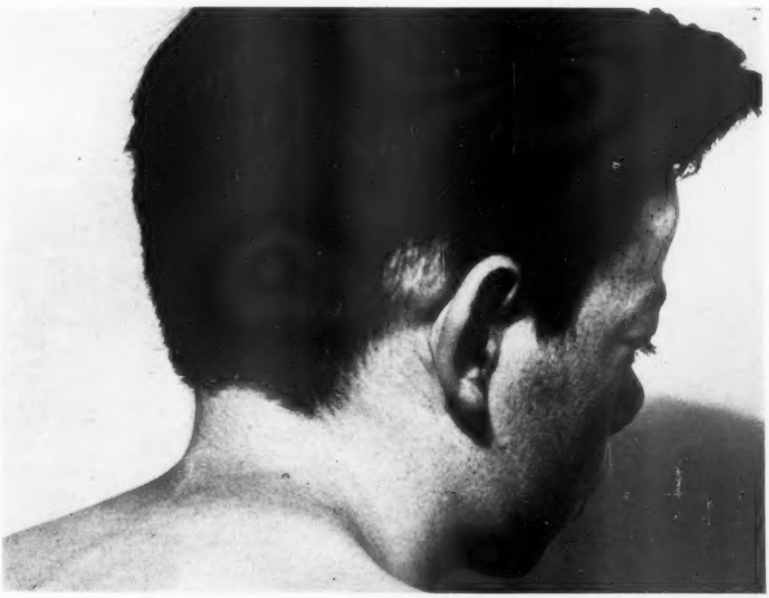

FIG. 4. Head of V-9 showing fibrous connective tissue mass behind ear

spotted yellow. Microscopic examination revealed longitudinal and cross-sectioned loose fibers which formed the bulk of the mass. Blood vessels, nerves, and foci of fat were scattered throughout. Another lesion about 1 cm. in diameter was removed from the center of the back. In the surgical procedure a smaller lesion about 0.5 cm. was also located and removed. These two specimens were diagnosed by the pathologist as "fibromas" (Fig. 5). Subcutaneous lumps had been observed on the body of V-9 by his close associates from his infancy. A projection in the medial region of the forehead of this patient at three months of age was illustrated in family photographs.

When examined, V-29, age 20, had at least two lesions on his body which,

on superficial examination, closely resembled those taken from V-7 and V-9, described above. One was located on the back of the right hand and one was below the right scapula. A similar mass had been removed from the shoulder several years earlier.

In addition to the six individuals described with intestinal polyps, osteomas, and subcutaneous lesions, one other (V-20), age 6, also had subcutaneous masses. Previous examination revealed minor bone changes of the type which may precede osteomas. No intestinal polyps were detected at proctoscopy. All

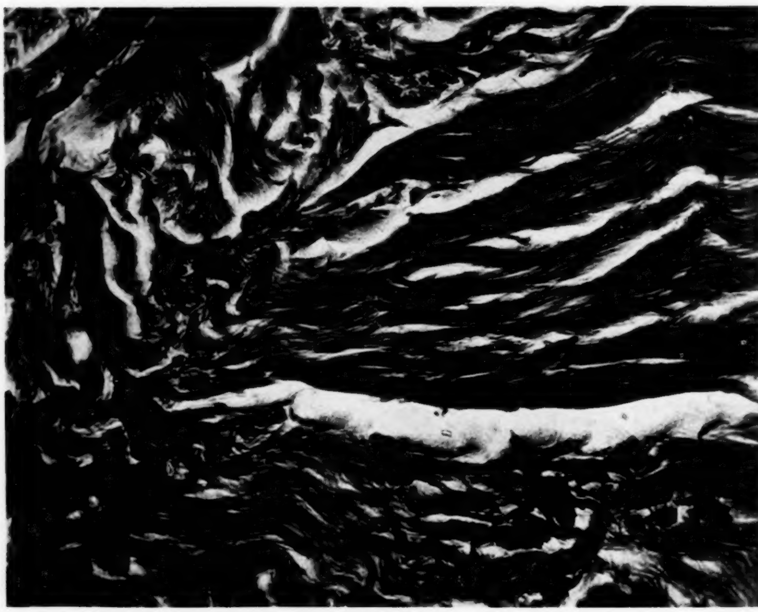

FIG. 5. Cross section of fibroma removed from V-9

other members of the group were interviewed and examined and found to be free from subcutaneous lesions of any kind. Close relatives were also interviewed and no history of such lesions was detected. Three manifestations of abnormal growth (polyposis, osteomatosis and subcutaneous lesions) were present in the same six individuals while all other members of the family group except V-20 were free from all three anomalies.

HISTORY OF DECEASED MEMBERS

All ancestral lines (Fig. 1) of the family group were studied as completely as possible. Evidence for the presence of the abnormalities discussed here was

found in only one branch of the kindred. Information concerning the deceased members of this branch is summarized in Table 1.

TABLE 1. EVIDENCE FOR INTESTINAL POLYPS, OSTEOMAS, AND SUBCUTANEOUS LESIONS AMONG THE DECEASED MEMBERS OF GROUP

INDIVIDUAL	DATE OF DEATH	AGE AT DEATH	INTESTINAL POLYPS	OSTEOMAS	SUBCUTANEOUS LESIONS	SOURCE OF INFORMATION
II-7	1909	53	Death from carcinoma of bowel	Unknown	Several	Relatives
III-1	1935	58	Colectomy performed; death from carcinoma	Unknown	Multiple	Relatives and friends
III-2	1921	41	Death from carcinoma of bowel	Hard irregularities on head	Multiple	Relatives and friends
III-3	1916	33	Death from carcinoma of rectum	Hard irregularities on head	Multiple	Relatives
III-4	1942	58	Suggested from symptomatic evidence	Unknown	Two said to have been removed	Relatives and friends
IV-1	1937	34	Positive diagnosis colectomy	Hard irregularities on head	Multiple. Two removed from back	Hospital records, relatives
IV-3	1929	22	Death from "intestinal flu"	None observed by relatives	None	Relatives
IV-5	1923	11	None. Accidental death	None observed by relatives	None	Relatives
IV-8	1940	35	Symptomatic. Death from carcinoma of rectum	Hard irregularities on head	Several. One or more removed	Relatives, photographs.
IV-9	1936	29	Positive diagnosis colectomy	Positive diagnosis and removal	Multiple cysts	Family, barber and relatives
IV-11	1941	29	None. Accidental death	None observed by relatives	None	Relatives
IV-15	1941	31	Symptomatic. Death from carcinoma of stomach and bowel obstruction	Multiple bony exostosis of scalp and forehead	Multiple	Relatives
V-11	1950	20	None	None observed	None	Examination, personal history

The oldest individual for whom definite positive evidence was available was II-7. She died in 1909 from carcinoma of the colon and was known to have "surface tumors." Her mother (I-3) had died in 1891 at the age of 64. Infor-

mation concerning the cause of her death was meager. The records in the mortuary from which she was buried recorded the cause of her death as "cancer." No death certificate or medical or hospital records were available. No one knew definitely whether or not she had "surface tumors." The descendants of I-1 and I-2 have been interviewed and examined when warranted. No polyposis, osteomatosis or "soft tumors" were detected. Likewise the descendants of I-3 by another husband and the descendants of I-4 by a second wife have been interviewed and examined. None of the three abnormalities here considered were detected.

The available evidence suggests that the same relationship between intestinal polyps, osteomas, and subcutaneous lesions observed among the living members of the group also existed in earlier generations. Eight of the thirteen deceased members were reported to have died with carcinoma of the colon and rectum. Presumably all of these individuals had multiple intestinal polyps. Pathological verification was available for two (IV-1 and IV-9). Six were reported to have had osteomas. Positive diagnosis was available for one (IV-9) of the six. Data were not available for two (II-7 and III-1). All eight who had carcinoma of the colon and presumably multiple polyposis were known to have had subcutaneous tumors or cysts.

INHERITANCE OF SUBCUTANEOUS LESIONS

The pattern (Fig. 1) of inheritance for intestinal polyposis (Gardner, 1951) and multiple osteomas (Gardner and Plenk, 1952) was characteristic of a dominant gene. Since the same individuals expressed both manifestations of abnormal growth and other members of the group were carefully examined and found to have neither abnormality, a single defective gene was postulated to account for intestinal polyps and osteomas. An alternative hypothesis would postulate separate but closely linked dominant genes for the two expressions.

The inheritance of the subcutaneous lesions was complicated by the different, apparently unrelated, kinds of abnormal surface growths occurring among the members of the group. Subcutaneous lesions were present in each individual with intestinal polyposis and osteomas. Other members of the group free from intestinal polyps and osteomas were interviewed and examined and found to be free also from subcutaneous lesions. Although different kinds of lesions occurred simultaneously, connective tissue masses probably were present (or removed) in all living individuals with subcutaneous lesions. It was difficult to visualize any connection between polyps of the colon, osteomas of the membraneous bones and subcutaneous masses. Yet the correlation in this family group was impressive and may represent more than a coincidence. Some fundamental gene-controlled process may have given rise to all three manifestations. The alternative hypothesis involving three or more closely linked genes should also be considered.

In another kindred (No. 134 in the records of the Laboratory of Human Genetics, University of Utah) intestinal polyposis has been found to follow a dominant pattern of inheritance but no osteomas nor subcutaneous lesions have been identified. Epidermoid cysts were found to follow an hereditary pattern in two other large kindreds (No. 77 and No. 184) but no cases of polyposis nor osteomas were detected. In the kindred (No. 109) under discussion these abnormal growths occurred in only one branch. Members of other branches have been interviewed, examined and found to be free from all three manifestations. If a single gene is involved it must behave differently from those genes postulated for kindred 134, 77 or 184. Either different genes or modifiers in the genetic environment may account for the different genetic action in the different kindreds. A new dominant mutation expressing itself first in I-3 or II-7 is suggested to account for the origin of the defective gene in kindred 109.

The literature includes several cases of hereditary tumors and cysts. Syndromes such as "epiloia" including different kinds of tumors along with other abnormalities have been described. None seem to fit the present case in which intestinal polyposis, osteomas and subcutaneous lesions occur simultaneously in the same individuals in one branch of a large kindred. This combination may prove valuable for control of cancer following intestinal polyposis in kindred 109. Since the bone and subcutaneous abnormalities seem to occur early in the individuals destined to become afflicted with polyposis, early diagnosis and treatment may be facilitated.

SUMMARY

Fifty-one members of a family group were examined for subcutaneous tumors and cysts. Seven were positive and forty-four were negative. Six of the positive patients were shown by previous examinations to have multiple intestinal polyps and multiple osteomas. The other was a child who also had minor bone changes but no intestinal polyps. Other members of the group were examined and found to have no intestinal polyps, osteomas, nor subcutaneous lesions. The lesions were of three kinds, epidermoid, cysts, fibromas and ill-defined masses of connective tissue. Different kinds were present in the same individuals. Fibrous connective tissue masses were probably present in all positive cases. Pathological evidence is available for three patients. A dominant mode of inheritance was interpreted for all three manifestations. A single defective gene arising from a mutation is postulated to account for the abnormalities in this family group.

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Elimination of Recessive Lethals from the Population when the Heterozygote can be Detected.[1]

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INTRODUCTION

ATTENTION has recently been called by Neel (1947) (1949) to the possibility of detecting the heterozygote in the case of recessively determined diseases, and to the potential application of such knowledge. The possible uses for such information may be dichotomously grouped into (1) physiological studies or investigations of gene action, and (2) eugenical applications. This paper is concerned with a particular eugenical use and its consequences.

The general aim of eugenics in the case of any particular hereditary disease is to eliminate that undesirable trait from the population. This may be accomplished either by selection against the mutant gene, or by the employment of a special mating system preventing the production of the morbid genotype. In the case of a recessively determined disease, where the heterozygote is recognizable, both methods become highly efficient. This paper will treat the case of selective mating in such situations.

METHODS

The general type of trait to be considered will be a lethal one showing a clear cut case of a simple pattern of recessive inheritance. That is, AA and Aa, although separable phenotypically, are equal in viability and fertility, while aa is lethal. By setting up a mating system in which the only matings permitted are AA x AA and AA x Aa, the further appearance of aa genotypes will be greatly reduced. Three cases of this model will be considered, with the mutation rate being the only variable. In all cases selection and migration are assumed to be absent, population size is assumed to be large and constant (thereby making the effects of drift negligible), and mating is monogamous.

RESULTS

Case 1. No mutations.

In a population consisting only of AA and Aa as would be the case here, and where $AA + Aa = 1$, the frequency q, of a, is equal to one-half the propor-

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[1] This work was done while the author was a holder of a U. S. Public Health Service Post-Doctoral Fellowship.

tion of Aa. Setting the frequency of a equal to q, the proportion of Aa is $2q$, and that of AA is $(1–2q)$. The value of q in such a population obviously cannot exceed one-half, and it will be shown later that under this special mating system, the actual limit of q is lower still.

Then if the only matings permitted are AA x AA and AA x Aa, the gene and genotypic frequencies will remain constant under the conditions given here. The matings, their frequencies, and the relative proportion of AA and Aa offspring produced by them are given below: it will be seen that the proportion of AA and Aa among the offspring is the same as that in the parental generation:

Mating	Frequency	Offspring AA	Aa
AA x AA	$(1 - 2q) - (2q)$	$1 - 4q$	0
AA x Aa	$2(2q)$	$2q$	$2q$
Total	1.00	$1 - 2q$	$2q$

Before going on to the next case, it will be worthwhile to point out an interesting aspect of this system, which, while not very likely to occur under this static model, will actually be a limiting condition for the two subsequent models to be discussed. If, at the initiation of this mating system, $2q > 1–2q$ or $Aa > AA$, then all of the AA will be mated with Aa, and that excess of Aa over AA will not find mates. The mating table for this situation would be as follows:

Mating	Frequency	Offspring AA	Aa
AA x AA	0	0	0
AA x Aa	$2(1 - 2q)$	$1 - 2q$	$1 - 2q$
Total	$2 - 4q$	$1 - 2q$	$1 - 2q$

It is seen that $Aa = AA = 0.5$ among the offspring, and therefore q is 0.25. These are the limits for the genotypic and gene frequencies of the heterozygote and recessive gene, under this selective mating system. In this situation, the maximum proportion of couples permitted offspring, as compared to the case in which there is no restriction with respect to genotypes, is reduced by the proportion $4q - 1$, the excess of Aa over AA. This, of course, results in an equivalent reduction in population size of the subsequent generation.

Case 2. Mutation one way ($A \rightarrow a$).

In a large random mating population where aa is lethal, and mutations occur only from A to a at a rate of u per generation, an equilibrium will be reached between the opposing pressures of mutation and selection. As is well known, the frequency of a (q) at equilibrium is given by the following formula:

$$q = \sqrt{u}$$

However, in the case of the special mating system under consideration, selection pressure is eliminated, and therefore, at first glance, one might conclude that the limiting value of q would be unity. This, however, is not correct, for, as will be recalled from case 1, it was shown that the limiting value of q under this mating system is 0.25.

The mutation process of $A \rightarrow a$ will still continue, of course, even when the limiting value of q is reached. This will result in reduction in population size in the same way as was shown in the special case (1) where $Aa > AA$. The mutations would lead to the production of genetically Aa and aa individuals, who would still be phenotypically either AA or Aa. With mutation rate u, and $AA = Aa$, the makeup of the mating population would be as follows:

Phenotypes	
AA	Aa
$2uAa$	uaa
$(1 - 2u)AA$	$(1 - u)Aa$

The mating table for this generation would then be:

Mating	Frequency	Offspring AA	Aa	aa
Aa x aa	$2u^2$	0	u^2	u^2
Aa x Aa	$2u - 2u^2$	$.5u - .5u^2$	$u - u^2$	$.5u - .5u^2$
AA x aa	$u - 2u^2$		$u - 2u^2$	
AA x Aa	$1 - 3u + 2u^2$	$.5 - 1.5u + u^2$	$.5 - 1.5u + u^2$	
Total	1.00	$.5 - u + .5u^2$	$.5 + .5u - u^2$	$.5u + .5u^2$

Disregarding the u terms because of their negligible magnitude, it can be seen that the decrease in population size per generation would be approximately $2u$, $1.5u$ (the excess of Aa over AA) not being permitted to have offspring, and the remaining $.5u$ proportion of the individuals being lethal aa. It is of special interest to note, that at what may be roughly called the equilibrium point of this selective mating system, the expression of the lethal gene, a, attains half the frequency characteristic of it at the equilibrium point under natural selection.

In view of these rather interesting general results, it seems worth while to calculate some estimates of the time required for these changes to take place. In order to do this, assumptions will have to be made as to the frequency of a and the magnitude of u (mutation rate from $A \rightarrow a$). For the value of a (q) I will assume 0.01, which, incidentally, has been given as an estimate of the gene frequency for Tay Sachs disease in the Jewish population (Slome 1933). This value may be somewhat higher than the frequency of most mutant genes, but since the magnitude of u is by far the main determiner of the rate of change of q, the specific value of q is not critical. For u I will use two values, 5×10^{-5} and 1×10^{-4}, both of which have been reported as mutation rates for various

mutant genes in human populations. Calculations of the time in generations required for q to reach values of 0.05, 0.01, and 0.25 on the basis of the above assumptions are shown below:

	Time in Generations (approx.) to Reach q of:		
u	0.05	0.01	0.25
5×10^{-5}	800	1900	5500
1×10^{-4}	400	900	2700

The formula used for these calculations is

$$q_n = 1 - (1 - q_0)e^{-un}$$

where q_n is the frequency of q in the n^{th} generation, q_o is the initial frequency of q, and n is the number of generations for the given change in gene frequency to occur.

Case 3. Mutations both ways.

In a large random mating population, where selection is not operating and mutation occurs from $A \rightarrow a$ at rate u and from $a \rightarrow A$ at rate v, the equilibrium value of q is determined by the two mutation rates u and v. The equilibrium value for q is simply:

$$q = \frac{u}{u + v}$$

In the mating system under consideration here, it has already been shown that the limiting value of q is 0.25, and therefore, it becomes of importance to examine the probable range within which q would be expected to fall. For if q, as determined by the above formula, exceeds 0.25, it would mean that the resultant mutation pressure, after q reaches its limiting value, would still be in the direction $A \rightarrow a$, thereby leading to a decrease in population size.

In order for q to be $\leqq 0.25$, $v \geqq 3u$. The few observations that have been made of the rates of reverse mutations, have all been less than their respective u's, and so it appears that the critical situation described above is to be expected. At this point (i.e., $q = 0.25$), it can be shown that the reduction in population size per generation will be approximately $2u - v$. In view of this interesting and somewhat unexpected result, it again seems appropiate to make some estimates of the time required for q to reach various values. For simplicity, I have assumed that $u = v$ even though u is usually much greater than v. The calculations are carried out with $q = 0.01$, and $u = v = 5 \times 10^{-5}$ and 1×10^{-4}. The formula used is

$$q_n = \frac{u}{u + v} - \left(\frac{u}{u + v} - q_0\right)e^{-n(u+v)}$$

the results are presented below:

u	Time in Generations (approx.) to Reach q of: 0.05	0.01	0.25
5×10^{-5}	850	2000	6700
1×10^{-4}	425	1000	3400

It can be seen that the presence of reverse mutations, even at the exaggerated rate assumed here, does not cause an appreciable change in the rate of change of q when compared with case 2 where reverse mutations were assumed to be absent.

DISCUSSION

In view of the interesting equilibrium condition of this mating system, it appears of importance to consider briefly its feasibility.

The first point to be noted is that the expression of the mutant gene at equilibrium, under this system, (case 2 and 3) would still attain half the frequency characteristic of its equilibrium value under natural selection. In consideration of the difficulties involved in carrying out such a mating plan, the above gain would hardly seem to be warranted. Secondly, at the equilibrium point, a certain amount of artificial selection would have to be practiced, since there would be an excess of *Aa* over *AA* due to mutation, and these individuals would not be permitted to have offspring. Finally, and probably most important, as the frequency of q approaches its limiting value, the restriction of mating combinations tends towards an almost intolerable situation. For example, when $q = 0.25$, each person would have to find a mate among one-half of the persons otherwise available. Then, if we consider the case where n gene pairs are concerned, each responsible for a separate lethal trait, at equilibrium each person would have to find a mate among $(\frac{1}{2})^n$ of the persons otherwise available. Under such conditions, the enforcement of the necessary mating restrictions would almost become impossible.

It would appear, then, that the elimination of *aa* genotypes from the population by the use of a selective mating system alone is highly impractical, if not impossible.

SUMMARY

The consequences of a mating system in which *Aa* x *Aa* matings are not permitted and *aa* is lethal have been examined under three sets of conditions. In all cases, the population is assumed to be large, fixed in size, and with migration absent.

Case 1. No mutation. Gene and genotypic frequencies remain fixed at what they were in the initial parental generation of the mating system.

Case 2. Mutation one way ($A \rightarrow a$). The frequency of a (q) increases to its limiting value (0.25) and then reduction in population size ensues at a rate

proportional to $2u$. The frequency of *aa* attains half the frequency characteristic of it under natural selection.

Case 3. Mutation both ways. The same phenomena takes place as in case 2, but at a slightly slower rate.

The implications of these results have been briefly discussed in view of the possible proposal of such a mating system in human populations.

ACKNOWLEDGMENT

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Data Pertaining to the Population Dynamics of Sickle Cell Disease[1]

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INTRODUCTION

UNDER CONDITIONS of low oxygen tension, the erythrocytes of certain Negroes assume bizarre shapes, the so-called sickling phenomenon. The great majority of individuals whose erythrocytes can be induced to sickle appear to suffer no ill effects. They are spoken of as having the sickle cell trait, or sicklemia. Occasionally, however, an individual is encountered in whom the sickling phenomenon is the basis for a severe, chronic, hemolytic anemia, known as sickle cell anemia. Genetic studies on Negroes living in the United States have shown that the tendency of the red blood cells to sickle is inherited as if due to a single gene. The distribution of the sickle cell trait and sickle cell anemia within families leaves little room for doubt that in the majority of cases, the two are related as heterozygote to homozygote (Neel, 1947, 1949, 1951a; Beet, 1949).

Sickle cell anemia is a serious disease, the various clinical manifestations of which have recently been reviewed by Margolies (1951). In our own experience the reproductive expectation of children with sickle cell anemia in the United States has in the past been greatly reduced, to perhaps 20 per cent of normal. Approximately 10 per cent of Negroes living in the United States have the sickle cell trait. From this it may be calculated that the frequency at birth of sickle cell anemia among American Negroes should be approximately 2.8 per 1000 births.

Numerous studies in Africa have revealed a very considerable range in the frequency of the sickling phenomenon among different types of Negroes (summary in Neel, 1951b). Roughly speaking, the observed frequency of the sickling phenomenon is highest in a belt extending across the middle third of Africa, with lower rates to the north and south. In this middle belt of Africa, the average frequency of the sickling phenomenon among different tribes is in the neighborhood of 20 per cent.

If homozygosity for the gene responsible for the sickling phenomenon has the same consequences in the African as in the United States Negro—i.e., if

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sickle cell anemia as we know it in this country occurs in Africa with the frequency suggested by a 20 per cent incidence of the sickling phenomenon—then some very interesting questions of population genetics arise. How is a gene frequency of this order of magnitude maintained in the face of such strong negative selection?

In the light of the known frequency of the sickle cell trait in Africa, there has been in the past a relative paucity of case reports of sickle cell anemia emanating from that country. Several investigators have drawn attention to this fact, and postulated that some modification of the above described genetic theory is necessary (Raper, 1950; Lehmann, 1951). More specifically, Raper (1950, 1951) has suggested that "the appearance of sickle-cell anaemia depends, not only on the extent to which the trait is present in a community, but also on the extent to which admixture with other genetic strains has occurred." This general concept has recently been developed in a genetically somewhat more sophisticated fashion by Ashman (1952).

The situation has been complicated by the discovery that in addition to the usual type of sickle cell anemia, developing on the basis of homozygosity for the gene responsible for the sickling phenomenon, there are at least three other genetic types of sickle cell anemia, all much less common than the first-mentioned type, each developing on the basis of heterozygosity for the sickle cell gene and for another gene which also affects the characteristics of the red blood cell (review in Neel, 1952; Neel, Itano and Lawrence, 1953). The recognition of these additional types of sickle cell anemia serves to intensify the potential problem in population genetics, since their existence should increase the selective pressure against the gene responsible for the sickling phenomenon.

Elsewhere the present author (Neel, 1952) has reviewed the steps which might be taken to determine whether the results of homozygosity for the gene responsible for the sickling phenomenon are the same in Africa as in the United States. These steps, in brief, are:

1. A comparison of the results of quantitative electrophoretic studies of the hemoglobin of individuals exhibiting the sickling phenomenon in Africa and the United States, it having been shown that a variable proportion of the hemoglobin is electrophoretically abnormal in sickle cell anemia and the sickle cell trait (Pauling et al., 1949, et seq.).

2. The analysis of the results of the three types of marriages, normal x normal, normal x sickle, and sickle x sickle, among native Africans.

3. Further casuistic studies among African natives.

4. An analysis of the relationship among Negroes residing in the United States between the apparent amount of white admixture and the occurrence and severity of sickle cell anemia.

The present paper will be primarily devoted to this latter approach to the

problem, but certain other data also pertinent to the question of the population dynamics of sickle cell anemia will be presented. Two hypotheses will be tested:

1. Admixture with non-Negroid ethnic groups is, in the United States, a contributing factor in the development of clinically recognizable sickle cell anemia. Under this hypothesis, in the United States only a fraction of persons homozygous for the sickling gene develop sickle cell anemia. These are usually persons who have received certain genetic "modifiers" or iso-alleles of the "sickling" gene from Caucasian or Indian ancestors. There is a considerable range in the amount of non-Negroid ancestry in the American "Negro;" the studies of the social anthropologist suggest that the average non-Negro component is about one-third (Herskovits, 1942; Ashley Montagu, 1944; Meier, 1949). This estimate is confirmed in general by the relative frequency of sickling in African and United States Negroes. If, now, admixture with other ethnic groups is a contributory factor to the development of sickle cell anemia, it follows that the average individual with clinical sickle cell anemia should be somewhat less Negroid than the average United States Negro, since included in the latter group are persons with little or no non-Negroid ancestry.

2. There is a positive correlation between the apparent clinical severity of the sickle cell anemia and the amount of non-Negro ancestry. Under this hypothesis, it is assumed that the chance of an individual possessing those genetic modifiers or iso-alleles which influence unfavorably the results of homozygosity for the gene responsible for the sickling phenomenon are more or less directly proportional to the amount of non-Negroid ancestry.

METHODS

Neither the estimation of the amount of non-Negroid ancestry nor of the severity of sickle cell anemia is an easy matter. Undoubtedly there are those who will take exception to the procedures adopted in this paper. At the moment, however, no more workable approach to the problem comes to mind.

The procedure followed in roughly evaluating the amount of non-Negroid ancestry was as described by Dr. F. Thieme (1952), to whom we are indebted for considerable discussion on this point. In brief, an "ethnic factor" has been calculated for each Negro included in this study. This "ethnic factor," with a theoretic range from 4 to 64, has been calculated by rating each individual as to depth of skin pigmentation (1 to 32), amount of hair curl (1 to 16), lip thickness (1 to 8), and nose shape (1 to 8), and cumulating the scores into one final "ethnic factor," a score of 64 being characteristic of an extreme Negroid type. In judging the depth of skin pigmentation, use was made of the chart of skin color published by Gates (1949). The nine shades of coloring which appear on that chart were assigned the following quantitative values: 1–31, 2–28, 3–25, 4–18, 5–15, 6–12, 7–8, 8–5, and 9–2. All ratings were carried out by a trained

field investigator (Mrs. Catharine Williams) after a preliminary indoctrination period during which it was established that the ratings assigned by the investigator and the author seldom differed by more than two or three points.

This method of evaluating the amount of Negro ancestry involves no assumptions concerning the relative contributions of Caucasian and Indian intermixture to the non-Negroid component. By and large, a given amount of Indian ancestry would probably lower the ethnic factor less than the same amount of Caucasian ancestry. Since, however, conclusions are based on relative rather than absolute values, the precise proportions of Indian and Caucasian ancestry are immaterial for the purposes of the present argument.

The evaluation of the over-all severity of a chronic anemia such as this is also difficult. The criteria for the diagnosis of the disease have been presented in detail elsewhere (Neel, 1951a; Margolies, 1951). Sickle cell anemia is subject to periodic exacerbations, termed crises, often provoked by infections of one kind and another, during which the disease may appear especially severe. These exacerbations are a frequent cause of hospital admission. For this reason, a study of hospitalized patients seemed interdicted. Rather, with a few exceptions, all the subjects of this study were seen in their homes or in the course of routine out-patient follow-up, and were in the "quiescent" phase of their disease. It is obvious that even during the "quiescent" phase there may be subclinical exacerbations. The most immediately apparent criterion of the severity of an anemia is the hemoglobin level, and this has been used as one of the criteria of this study. However, hemoglobin level represents a balance between the rate of erythrocyte destruction and erythrocyte proliferation. Two individuals with the same hemoglobin levels may have marked differences in the severity of their hemolytic processes, the individual with the more severe hemolytic process maintaining his hemoglobin by virtue of a more active hematopoietic response. The latter is conveniently measured by the reticulocyte count, and this was made the second measure of the severity of the anemia. In view, however, of the response of the reticulocyte to fluctuations in the severity of the hemolytic process which may escape the level of clinical significance, findings with respect to the reticulocyte count must be interpreted with great caution.

Sickle cell anemia is not infrequently a cause of death. Probably the single most significant observation which could be made would be a comparison of the ethnic factor of individuals dying of sickle cell anemia with that of those surviving, and with that of the general Negro population. Unfortunately, such a comparison is not practical. In this connection, it should be pointed out that the group of persons with sickle cell anemia upon whom these observations are based is a selected group, to the extent that it represents the survivors of an original group, some members of which have already died of the disease.

THE RELATION OF THE ETHNIC FACTOR RATING TO THE OCCURRENCE AND SEVERITY OF SICKLE CELL ANEMIA

A total of 45 patients with sickle cell anemia were scored with respect to the "ethnic factor." A marked preponderance of the subjects were in the first two decades of life. The findings are summarized in Figure 1a. The mean of all observations was 41.94 ± 1.02. One hundred and four controls of comparable background, age, and sex, selected at random without reference to the sickling phenomenon, were scored. The findings are given in Figure 1b. The mean value was 39.81 ± 0.76. The difference, 2.13 ± 1.27, is not significant, and, further, is in the opposite direction of that demanded by hypothesis 1 as outlined above. In this connection, it should be pointed out that inasmuch as the sickling trait is only very rarely encountered in non-Negro groups, it is to be expected that if the penetrance of the trait is relatively unaffected by genetic and environmental modifiers, then the more Negroid the individual, the greater the probability of encountering the manifestations of the sickle gene. If sickle cell anemia is due to the presence of two sickling genes *regardless of the degree of racial admixture*, then in America persons with the disease would be expected to be somewhat more Negroid than the average. The difference between the two sets of observations, although insignificant, is in a direction consistent with this expectation. In passing, it may be suggested that the conclusion of Hodges (1950) that "the incidence of erythrocytic sickling is less in 'pure' Negroes than in those with small admixtures of white and American Indian ancestry" appears to be based on a faulty statistical treatment of his data.

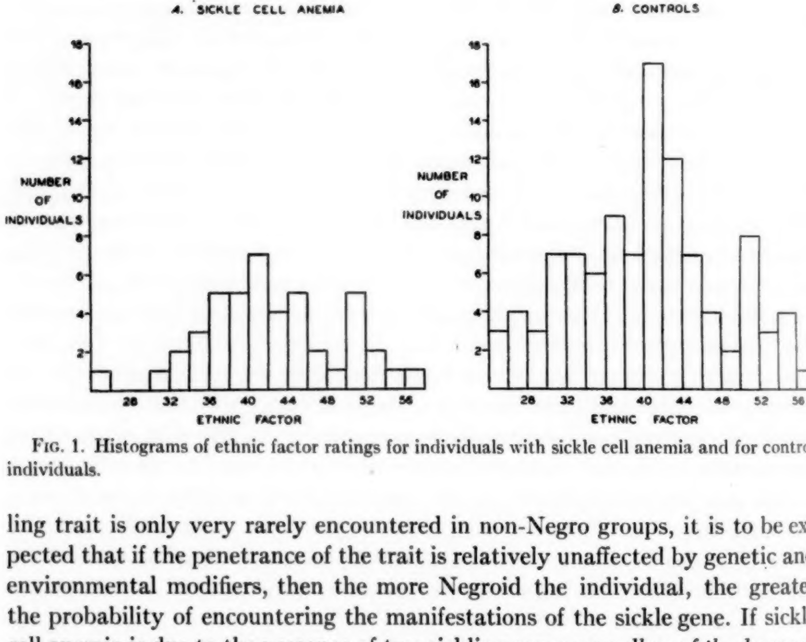

FIG. 1. Histograms of ethnic factor ratings for individuals with sickle cell anemia and for control individuals.

Figures 2 and 3 are scatter diagrams involving ethnic factor and grams of hemoglobin per 100 cc. of blood, and ethnic factor and percentage of reticulo-

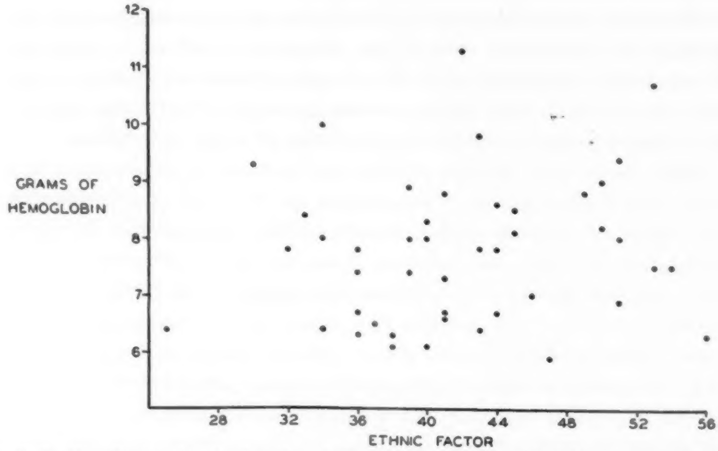

FIG. 2. Scatter diagram illustrating the relationship in patients with sickle cell anemia between ethnic factor rating and grams of hemoglobin per 100 cc. of blood.

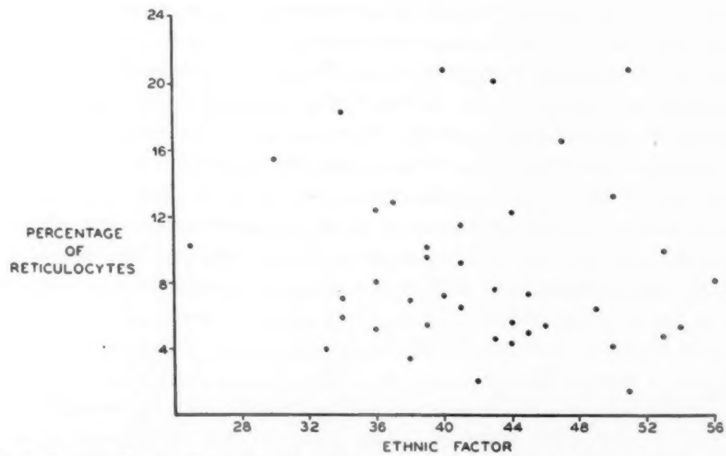

FIG. 3. Scatter diagram illustrating the relationship in patients with sickle cell anemia between ethnic factor rating and percentage of reticulocytes.

cytes among 1000 erythrocytes. The correlation of ethnic factor with hemoglobin is 0.101 ± 0.148. The correlation of ethnic factor with reticulocyte count is -0.126 ± 0.156. The latter correlation is based on 40 rather than 45 cases,

satisfactory interval reticulocyte counts not being available for five persons. Neither of the correlations is significant, although both are in the direction of a more severe hemolytic process in less Negroid persons. The numbers involved are small, on the borderline of the profitable use of a correlation coefficient, but can perhaps be excused in view of the difficulties involved in establishing a larger case roster of patients with this uncommon disease. So far as these data go, then, they lend no clear support to the hypothesis that racial admixture is causally related to the occurrence and severity of sickle cell disease.

As noted above, case reports of sickle cell anemia in Africa have been less common than might have been anticipated on the basis of experience in this country. However, several recent, careful studies suggest that the frequency of the disease may be more common than previously recognized. Reference should be made in particular to the beautiful studies of the Lambotte-Legrands in the Belgian Congo (1951; see also Foy, Kondi, and Hargreaves, 1952). These data, plus those presented in this paper, tend to suggest that the genetic basis of sickle cell anemia in Africa does not differ essentially from that of sickle cell anemia in the United States. Further studies on this question along the other lines indicated above are highly desirable.

Because of the increased mortality among individuals with sickle cell anemia living in the United States, there exists in the Negro population at large in this country less of the disease than predicted on the basis of gene frequency theory. Assuming for the moment a basic similarity in the genetics of the disease on the two continents, the frequency of the disease at birth in Africa should be approximately four times the United States frequency. However, again in consequence of differential mortality, there may also exist in the African population at large considerably less of the disease than suggested by gene frequency theory, and, in fact, no more of the disease than in the United States. Our own studies revealed a slight deficiency of sickle cell anemia from expectation in families in which the trait was segregating, but a relatively high frequency of abortions, miscarriages, and stillbirths, raising the possibility of a semi-lethal effect in utero (Neel, 1951b). If this effect actually occurs, it could be more prevalent in native Africans. Furthermore, individuals with sickle cell anemia could have a shorter life expectancy in Africa than in the United States. This might be due both to an increased probability of death from the manifold effects of sickle cell anemia *per se* and to disease suceptibilities conditioned in part by the severe anemia. In this connection, several investigators have suggested that persons with sickle cell anemia are especially susceptible to tuberculosis (Herrera Cabral, 1950; Weiss and Waife, 1952); there may be comparable and unrecognized susceptibilities to other diseases prevalent in Africa.

"BALANCED POLYMORPHISM" VS. HIGH MUTATION RATE

If, now, the genetics of sickle cell anemia are essentially the same in the two continents, we are confronted with some truly puzzling problems of population

dynamics. The two principal alternatives (or some combination thereof) which must be considered in explanation of the relatively high gene frequency are:

1. "Balanced polymorphism." This explanation assumes that the net fertility of heterozygotes with the sickle cell trait is slightly greater than normal, as well as much greater than that of individuals with sickle cell anemia. This provides a mechanism offsetting the loss of sickling genes because of the reproductive handicap of persons homozygous for the sickling gene. In a broad sense this explanation could include the "reproductive over-compensation" of the parents of defective children to which Glass (1950) in particular has drawn attention.

2. High mutation rate. This explanation assumes that the loss of genes through natural selection is offset each generation by mutation resulting in more sickle cell genes. A substantial barrier to the ready acceptance of this theory is the fact that not only is the mutation rate which must be postulated higher than any now recognized in human genetics, but this high rate is restricted to a very limited segment of the world's population.

If "balanced polymorphism" is the explanation, then it requires an average increased fertility on the part of the heterozygote of only 1 or 2 per cent—depending on the precise gene frequency and amount of negative selection—to offset the loss of genes through homozygosis. While studies in the United States could be suggestive, in the final analysis the critical data must come from Africa, since it is there that the situation has arisen, and living conditions are so different in Africa and the United States. There is no present evidence for this possibility. In six studies on the relation of age to the frequency of the sickling phenomenon, three studies carried out in Africa and three in this country, the frequency of the sickling phenomenon appeared to diminish with age. The magnitude of the trend was such as to raise the question of selection against the trait as well as the anemia, although there are alternative possible explanations (summary in Neel, 1951a). In this connection it should be noted that Lehmann (1951) on the basis of his personal experience questions this age trend, and feels it "unlikely that in Africa homozygotes suffer from sickle-cell anaemia, die early, and thus escape observation."

The possibility that a relatively high mutation rate is at least in part responsible for the frequency of the disease can readily be explored from data collected in this country, although for reasons to be mentioned later, a precise treatment of the problem is not feasible at the present time. In the absence of mutation, both of the parents of a child with sickle cell anemia, or one of the parents of a child with the sickle cell trait, are expected to sickle unless:

1. the gene responsible for the sickling phenomenon is occasionally non-penetrant,

2. the legal parents do not correspond to the biological parents,

3. the non-sickling parent has contributed a gene or genes which in conjunc-

tion with the sickle cell gene derived from the other parent produces a clinical picture identical with that produced by homozygosity for the sickling gene, or

4. there are technical failures in eliciting sickling.

With modern techniques for eliciting sickling, exceptions due to possibilities 1. and 4. are apparently quite rare. There is, on the other hand, clear support for the importance of factors 2. and 3.

In the course of the past four years, studies have been carried out in this laboratory on 122 different kindreds in which segregation for the sickling phenomenon was occurring. The findings in 75 of these kindreds have been published previously (Neel, 1951a); the data on the remaining 47 kindreds have not been previously discussed. A particular effort has been made to obtain blood specimens from both the parents of each child studied because of the occurrence of sickle cell anemia or the sickle cell trait. Thus far it has been possible to examine *both* parents of 49 sibships in which sickle cell anemia was segregating, and *both* parents of 22 sibships in which the sickle cell trait was present. Typing as to the A_1A_2BO, MN, and Rh (C, D, E, c) factors has been routine. The results are given in Table 1. Out of a total of 71 tests of both parents, 8 "exceptional" families have been encountered, in which only one of the

TABLE 1. A SUMMARY OF THE "EXCEPTIONAL" FAMILIES ENCOUNTERED AMONG 71 FAMILIES IN WHICH SEGREGATION FOR SICKLE CELL ANEMIA OR THE SICKLE CELL TRAIT WAS STUDIED. FURTHER DETAILS IN TEXT

	NUMBER OF FAMILIES STUDIED	NUMBER IN WHICH ONE PARENT FAILED TO SICKLE	EXPLANATION	EXCEPTIONAL PARENT
Sickle Cell Anemia				
Both parents tested for sickling; one child with sickle cell disease.	32	6	2 hemoglobin-*c* 1 non-paternity 3 unexplained	2 fathers 1 father 2 fathers, 1 mother
Both parents tested for sickling; more than one child with sickle cell disease.	17	1	1 hemoglobin-*c*	1 father
		NUMBER IN WHICH BOTH PARENTS FAILED TO SICKLE		
Sickle Cell Trait				
Both parents tested for sickling; one child with sickle cell trait.	7	1	1 unexplained	One of the two
Both parents tested for sickling; more than one child with sickle cell trait.	15	0		

parents of a child with sickle cell anemia exhibited the sickling phenomenon, or neither parent of a child with the sickle cell trait also had the trait.

It was mentioned earlier that clinical sickle cell disease might have several genetic bases. Far and away the most common is homozygosity for the gene responsible for the sickling phenomenon. The three other causes so far recognized are 1) simultaneous heterozygosity for the sickling and thalassemia genes, 2) simultaneous heterozygosity for the sickling gene and that responsible for hemoglobin-*c*, and 3) simultaneous heterozygosity for the sickling gene and that responsible for hemoglobin-*d* (bibliography in Neel, Itano, and Lawrence, 1953). The first situation can be recognized by the usual hematological studies. The second situation can be suspected on the basis of routine clinical and hematological studies (usually relatively mild course of disease in double heterozygote, striking increase in target cells in double heterozygote, significant increase in target cells in individuals heterozygous for the hemoglobin-*c* gene), but electrophoretic studies are necessary to an exact diagnosis. Finally, the third situation can thus far be recognized only on the basis of electrophoretic studies.

Certain of the present studies were carried out before the introduction of the techniques of electrophoresis into the analysis of inherited anemias, and for this and other reasons, it has not been possible to carry out electrophoretic studies on the non-sickling parent or parents in all eight of our exceptional families. However, such studies have been carried out for four families. These four families were not selected at random. Two of them were families in which the atypical findings mentioned above as characterizing the double heterozygote for the sickling and hemoglobin-*c* genes were observed; it was in fact the study of these two families which led to the discovery of hemoglobin-*c* (Itano and Neel, 1950; Kaplan, Zuelzer and Neel, 1951). In these two families, then, the cause of the apparent exception was segregation for the gene responsible for hemoglobin-*c*. In the third exceptional family studied electrophoretically, hemoglobin-*c* was also the cause of the unusual findings, as might have been suspected from the increased frequency of target cells in certain members of the family. In the fourth family, the propositus was a child with "typical" sickle cell disease. The mother failed to sickle, and exhibited no hematological abnormalities. Electrophoretic studies of the mother revealed only normal hemoglobin.[2]

The remaining four families have not been studied electrophoretically. The propositus for three of these families was a child with sickle cell anemia; in each case it was the *father* who failed to sickle. In one of these three families, the putative father's paternity could be excluded on the basis of the MN blood groups (child N, mother N, putative father M). In the other two families,

[2] I am greatly indebted to Dr. Harvey A. Itano for the electrophoretic studies on this patient's blood.

there was no evidence for non-paternity. In neither instance did hematological studies on the non-sickling father reveal any evidence of other hematological abnormality. The propositus for the fourth family was a child with the sickle cell trait, neither of whose parents sickled. This child also had six non-sickling older siblings. The oldest of these six siblings presented a paternity exclusion on the basis of the MN groups. Inasmuch as the serological techniques employed in this study are approximately 50 per cent effective in the detection of non-paternity, then it follows that for each instance of non-paternity detected there should exist one undetected instance. Any attempt to apply that argument literally in the present study is vitiated by the small numbers involved.

In summary, then, among a total of 71 families in which the propositus was a child with sickle cell anemia or the sickle cell trait, four instances of what might be mutation have been encountered. In three of these, non-paternity is an alternative explanation, and should be given at least equal standing with the possibility of mutation, despite the negative results of paternity exclusion tests. In the fourth instance, paternity is not at question since the mother is the exceptional parent.

If one assumes that the frequency of the sickling gene is being maintained through mutation, and if one knows the selective disadvantage of the anemia, it is in theory a simple matter to estimate for the gene pool in existence at any time the ratio of genes arising through mutation in that generation to those already present in the preceding generation. The actual calculation is complicated, however, by our relative ignorance of the severity of the negative selection which exists in Africa, as well as by the question of the extent to which racial admixture may have altered the mutation rate. If we assume that in Africa homozygotes and heterozygotes together constitute 20 per cent of the population, then $p = 0.106$, with the frequency of homozygotes equal to 11.24 per 1000 births. Assuming a 20 per cent fertility on the part of these homozygotes, then each generation the gene loss is $.80 \times .01124 = .008992$, and the ratio of genes arising each generation through mutation to those already present is

$$\frac{0.008992}{0.106} = \frac{1}{11.8}$$

The place to look for evidences of mutation is among the parents of sibships in which only one child has sickle cell anemia or the sickle cell trait. The occurrence of two or more affected siblings in an "exceptional" family can only be explained by mutation if it occurred at an early stage in the development of the gonad, an unlikely event. In this connection, it is noteworthy that all our unexplained "exceptions" involve families in which only one child has sickle cell anemia or the sickle cell trait. Obviously, however, this is no argument against non-paternity.

It is theoretically possible to undertake an approximate calculation to determine how many "exceptions" one would expect to encounter if mutation provides the answer to the frequency of sickle cell anemia. Such calculations require a random collection of families segregating for the sickle cell trait and/or sickle cell anemia. Unfortunately, the present material is not random, an especial effort having been made to study *large* sibships, and so the data are not considered suitable for such a calculation.

THE ORIGIN OF THE SICKLE CELL GENE

At the time of this writing, the sickling phenomenon has been found to be present in considerable numbers of individuals in three non-Negroid ethnic groups rather widely separated in space, as follows:

a. Yemenite Jews (Dreyfuss and Benyesch, 1951)[3]

b. certain Dravidian-speaking inhabitants of southern India (Lehmann and Cutbush, 1952)

c. certain areas in Greece (Choremis et al., 1951; Caminopetros, 1952).

Studies on the first two groups reveal so low a frequency of the Rh_o gene that any considerable amount of Negro admixture seems excluded (Brzezinski et al., 1952; Lehmann and Cutbush, 1952). Rh_o gene frequency studies have not yet been carried out on the Greek groups in question. The findings with respect to the Indians have led to the suggestions that 1) the gene responsible for the sickling phenomenon has been transferred to this group and the African Negro from a common ancestor (Lehmann, 1952; Mourant, 1952), and 2) that the gene has originated independently in the African Negro and the Indian groups in question (Mourant, 1952). The first suggestion, while it appears to "solve" one question, that of the origin of the sickle cell gene, actually still leaves us with the problem of accounting for the appearance of the gene in a single ethnic group, and, further, raises the question of the striking increase and spread of the gene in the one group to which it was introduced, as contrasted with its fate in the other group. The differences in the present-day breeding structure of African and Indian communities could be of importance in this respect. There is at the moment no apparent common point of origin between the three non-Negro groups involved, nor does it seem likely that critical data on this point will soon be forthcoming. It should be obvious that if the appropriate intensive studies of African populations demonstrate an autochthonous source of sickle cell genes (mutation), then we may infer several independent foci of origin of the sickling gene. In view of the widely accepted finding that the genetic differences between ethnic groups tend to involve quantitative variations in the representation of various genes rather than the presence or absence

[3] Note added in proof: Recent work has failed to confirm this report (Dreyfuss, R., Ikin, E. W., Lehmann, H., and Mourant, A. E., 1952, An investigation of blood groups and a search for sickle cell trait in Yemenite Jews, Lancet 263:1010–1012).

of particular genes, we might on a priori grounds expect to find that the sickle cell gene has arisen in several different foci. The "balanced polymorphism" hypothesis, the "high mutation rate" hypothesis, and the explanation which draws on both hypotheses—all are so obviously susceptible to the direct experimental attack as to discourage further speculation. The observations necessary to a decision can be made nowhere but in Africa.

SUMMARY

1. A series of 45 American Negroes with sickle cell disease and 104 controls of comparable background, age, and sex have been given an ethnic rating based on skin color, hair form, and lip and nose structure. Individuals with relatively low ratings are thought to have more Caucasian and Indian admixture than individuals with relatively high ratings.

2. There was no significant difference between the mean ethnic ratings of individuals with and without sickle cell disease.

3. No significant correlation could be demonstrated between an individual's ethnic rating and the severity of the disease as judged by the hemoglobin level or the number of reticulocytes per 1000 erythrocytes.

4. Out of a total material of 122 kindreds in which segregation of the gene responsible for the sickling phenomenon was occurring, there were 49 sibships in which the sickle cell disease was present and both parents could be tested for the occurrence of sickling, and 22 sibships in which only the sickle cell trait was present and both parents could be tested.

5. There were seven exceptions to the general rule that both parents of a child with sickle cell disease show the sickle cell trait. In three instances the exceptional parent was found to be heterozygous for the gene responsible for another inherited abnormality of hemoglobin (hemoglobin-*c*). In one instance there was a paternity exclusion. The remaining three exceptions can be attributed to mutation or, in the two instances where the father was the exceptional parent, to undetected non-paternity.

6. There was one exception to the general rule that at least one parent of a child with the sickle cell trait will also show the trait. There was no evidence of non-paternity or of the segregation of any other gene affecting hemoglobin synthesis.

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An Investigation of 69 Cases of Exomphalos

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EXOMPHALOS is an uncommon congenital malformation, characterized by incomplete development of the abdominal wall, with herniation of the intestine. It results from incomplete reduction of the herniation of the mid-gut loop, which normally returns to the abdomen at about the 42 mm. stage of embryonic development. Small series of cases have been described by Gross and Blodgett (1940), O'Leary and Clymer (1941), Specht and Shryock (1943) and Hollenberg (1928), and larger series have been assembled from the literature by Hebert (1948) and O'Leary and Clymer (1941). These sources provide some information about incidence, sex ratio, associated malformations, and familial incidence. So far as we are aware the association of incidence with maternal age and birth order has not been examined.

We have attempted to obtain information about all cases of exomphalos, born to mothers domiciled in Birmingham in the years 1941–51, from (a) clinical and post mortem records of maternity, paediatric and general hospitals, and (b) registers of stillbirths and infant deaths kept by the Local Authority. 69 propositi (35 stillborn; 34 liveborn) were identified in 68 fraternities; in view of the serious nature of the condition it seems unlikely that any were missed. Additional data were obtained by field inquiry from 62 mothers of 63 propositi; details of these fraternities, as well as of 6 others in which the mothers were not interviewed, are given in the appendix. The diagnosis was confirmed at operation or post mortem examination in 28 cases, and from hospital records in 27. The other 14 patients were delivered at home, and the only available information about diagnosis was the record in the register of deaths.

The malformation was described fully in 27 of the 28 cases examined at operation or post mortem; other viscera (in addition to the intestine) present in the hernial sac were: liver (12 times); stomach (4 times); spleen (4 times); kidney (twice); bladder (once). In 7 of the 27 cases the hernial sac had ruptured before birth. In one unusual case the defect in the abdominal wall was situated to the right of a normal umbilical cord and the hernial sac contained small intestine only. A similar case, in which the sac contained omentum only, was recorded by Williams (1946).

INCIDENCE

The incidence of exomphalos in Birmingham 1941–51 was 0.31 per thousand total births, or 1 in 3200 (69 cases in 221,041 births). This is higher than the

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estimates of 1 in 10,000 and 1 in 5,000 derived from small numbers of cases by Hebert (1928) and Jarcho (1937) respectively.

SEX RATIO

Sex was doubtful in 2 cases in which the genital organs were malformed; among the remaining 67 the percentage of males was 51. In Table 1 sex ratios are given for exomphalos according to its association: (a) with anencephalus, 29% male (approximately the same as for anencephalus without exomphalos for which Record & McKeown (1949) reported 33% of males); (b) with other malformations, 50% male; and (c) with no other malformations, 61% male. Gross & Blodgett (1940) found 11 males and 10 females in a series of 21 cases, and O'Leary and Clymer (1941) reported about twice as many males as females in a series of 88 cases, taken mainly from the literature. Reasons are given below for believing that these series are unrepresentative.

TABLE 1. SEX RATIO IN 67 CASES OF EXOMPHALOS*

EXOMPHALOS ASSOCIATED WITH:	NO. OF MALES	NO. OF FEMALES	PERCENTAGE MALE
Anencephalus	4	10	29
Other malformation	11	11	50
No other malformation	19	12	61
Total	34	33	51

* In 2 of the original 69 cases sex was doubtful.

ASSOCIATED MALFORMATIONS

The appendix gives details of other malformations associated with exomphalos, which are classified in Table 2. When more than one other malformation was present cases have been classified under the more serious defect (for example 5 patients with anencephalus and spina bifida are shown under anencephalus). In certain cases (e.g. anencephalus) the diagnosis can invariably be relied on, but in others it is less reliable if no post mortem examination was performed.

Thirty-eight of the 69 individuals exhibited associated defects, most of which were serious. The incidence is higher than estimates published by O'Leary & Clymer (1941)—29 associated malformations in 91 cases, and by Gross & Blodgett—10 in 22 cases. Neither of these series can be regarded as representative, since the material was largely derived from surgical clinics, and hence stillbirths and early deaths were excluded.

The frequency of association of anencephalus with exomphalos is striking (20%), and has not so far as we are aware been noted previously. O'Leary & Clymer (1941) described two cases in which exomphalos was associated with

anencephalus, and two others in which it was associated with spina bifida. The incidence of diaphragmatic hernia, ectopia vesicae and severe genital malformation also appears to be unduly high, since these are all uncommon abnormalities. Association with diaphragmatic hernia and cardiac defect was noted

TABLE 2. MALFORMATIONS ASSOCIATED WITH EXOMPHALOS

EXOMPHALOS ASSOCIATED WITH:	NO. OF CASES	
	Examined at post-mortem	Not examined at post-mortem
Anencephalus	0	14
Spina bifida	2	2 (5)*
Diaphragmatic hernia	4	0
Ectopia vesicae	3	1
Mongolism	1	0 (1)
Harelip or cleft palate	1 (3)	0 (1)
Hydrocephalus	1	1
Genital malformation	0 (4)	1
Other malformations	0	7
All associated malformations	12	26
No associated malformation	7	24
Total	19	50

* Numbers in brackets give the numbers of individuals exhibiting a particular malformation who have been classified under other associated abnormalities.

TABLE 3. DISTRIBUTIONS BY BIRTH RANK

BIRTH RANK	AFFECTED		AFFECTED, ANENCEPHALUS & SPINA BIFIDA EXCLUDED		CONTROLS	
	No.	Percentage	No.	Percentage	No.	Percentage
1	28	41.2	19	38.0	405	36.1
2	17	25.0	14	28.0	342	30.4
3	8	11.8	5	10.0	162	14.4
4	5	7.3	4	8.0	107	9.5
5	4	5.9	3	6.0	55	4.9
6 and over	6	8.8	5	10.0	53	4.7
Total	68	100.0	50	100.0	1124	100.0

by McCrory & Bunch (1947) in 2 cases, and with severe genital malformation by Specht & Shryock (1943) in one case.

BIRTH RANK AND MATERNAL AGE

Tables 3 and 4 give distributions by birth rank and maternal age respectively of (a) 68 propositi for which the requisite data were available and (b) controls

selected by taking every 200th birth (liveborn or stillborn) in the city during the same years (1941–51).

Proportions of affected are higher than of controls in birth-ranks 1, 5 and '6 and over', although none of the differences is significant. A similar distribution was noted in anencephalus and spina bifida (Record & McKeown, 1949) and when 18 cases associated with these abnormalities are excluded (Table 3), differences between the proportions of affected and controls in birth rank 1 are reduced. Of the 18 cases which exhibited the two central nervous malformations, 9 were first born. The proportions of first born among all individuals with anencephalus or spina bifida in Birmingham during the same years were 52% and 50% respectively. It is concluded that except in the presence of anencephalus as an associated abnormality, the incidence of exomphalos is not related to order of birth.

TABLE 4. DISTRIBUTIONS BY MATERNAL AGE

MATERNAL AGE (YEARS)	AFFECTED		AFFECTED, ANENCEPHALUS & SPINA BIFIDA EXCLUDED		CONTROLS	
	No.	Percentage	No.	Percentage	No.	Percentage
17–21	9	13.3	6	12.0	113	10.0
22–26	17	25.0	14	28.0	346	30.8
27–31	13	19.1	7	14.0	320	28.5
32–36	16	23.5	11	22.0	218	19.4
37 and over	13	19.1	12	24.0	127	11.3
Total	68	100.0	50	100.0	1124	100.0

Incidence does however appear to be related to maternal age (Table 4) being high in the upper age groups. The difference between the proportions of affected and controls aged "37 and over" is 7.8 ± 4.0 per cent. Cases with anencephalus and spina bifida do not show this association, and when they are excluded the association with age is accentuated, the difference between affected and controls aged "37 and over" being now 12.7 ± 4.7 per cent.

On the numbers available we are unable to determine to what extent the association of exomphalos with maternal age is related to the association with other malformations whose incidence increases with age (e.g. mongolism and hydrocephalus). Of the 31 cases in which no other abnormality was present 5 (16%) were in the age group "37 and over".

FAMILIAL INCIDENCE

Information about siblings of propositi was complete in 62 fraternities. One fraternity (No. 11) contained two propositi, both of which exhibited exomphalos unassociated with another malformation. There was no instance of exomphalos

among the 150 members of fraternities who were not propositi. 56 siblings were born subsequent to the first propositus, and one (also a propositus) was affected. If the incidence in siblings were the same as in the general population (0.31 per 1000), the probability of at least one being affected in a sample of 56 would be about 57 to 1 against. This is perhaps an underestimate, since incidence appears to increase with maternal age, and a series of sibs born after propositi would in general have older mothers. The risk in subsequent sibs is undoubtedly low, but it would be unwise to assume it is no greater than in the general population of births, as was suggested by Jarcho (1937) and Stein & Gerber (1939). Gross & Blodgett (1940) reported that there were no affected relatives in families of 22 patients. Pancot & Gelle (quoted by O'Leary & Clymer, 1941) described the malformation in three successive foetuses of a syphilitic mother.

Information concerning first cousins of propositi was obtained from the 62 mothers of 63 propositi, fraternities not well known to the mother being excluded. Of the 622 cousins for whom data were acceptable, three exhibited malformations which were: anencephalus, exomphalos, and hare lip. The individual with exomphalos was a first cousin of the two propositi who were members of one fraternity (No. 11); 17 other first cousins were unaffected.

In view of the high mortality of exomphalos, investigation of incidence in parents is unlikely to be fruitful. The only related abnormality recorded was an umbilical hernia of moderate size in a mother; the condition was noted shortly after birth and was treated by operation.

There were no consanguineous marriages among the 62 for which the data were available.

The only other malformations recorded in the 150 sibs of propositi were spina bifida (twice) and anencephalus (once). In each of the three fraternities in which these malformations occurred, the propositus exhibited a central nervous malformation (anencephalus twice, and spina bifida with anencephalus once) in association with exomphalos.

SUMMARY

1. An attempt was made to obtain information about all cases of exomphalos delivered to mothers domiciled in Birmingham, 1941–51. 69 propositi (35 stillborn and 34 liveborn) were identified in a population of 221,041 births, an incidence of 0.31 per thousand total births.

2. Approximately equal numbers of males and females were affected (34 males and 33 females; in 2 cases sex was doubtful).

3. The incidence of associated abnormalities was high: of the 69 propositi, 20 exhibited malformations of the central nervous system (14 anencephalus), and 18 had other malformations, most of which were serious.

4. The incidence of exomphalos appeared to increase with maternal age, but

was unrelated to birth rank when cases associated with anencephalus and spina bifida were excluded.

5. In cases associated with anencephalus, the sex ratio and association with birth order were approximately the same as for anencephalus alone.

6. Data were recorded for 62 fraternities, one of which contained two propositi. There were no affected among the 150 members of the fraternities who were not propositi.

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For case records we are indebted to all Birmingham hospitals, in particular the Children's Hospital, and to the Maternity and Child Welfare Department of the city. We are also indebted to Miss M. S. Gradwell, M.A., who recorded family histories in the homes of patients.

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APPENDIX

NO. OF FRATERNITY	BIRTH ORDER	SEX	AGE OF MOTHER	ASSOCIATED MALFORMATIONS
1	3	♂	39	Bilateral harelip and cleft palate, polydactyly, Meckel's diverticulum (P.M.)
2	6	♀	35	—
3	1	♂	19	—
4	3	(?)	38	Malformation of external genitalia (stillborn).
5	5	♂	28	Talipes (stillborn).
6	2	♂	23	—
7	1	♂	23	Right inguinal hernia (twin).
8	1	♀	24	Diaphragmatic hernia (stillborn—P.M.)
9	1	♀	35	Anencephalus (stillborn).
10	1	♂	28	(Stillborn).
11	{2	♀	26	—
	{6	♀	32	—
12	7	♀	39	(Stillborn).
13	1	♂	23	—
14	1	♂	20	—
15	7	♂	32	—
16	7	♀	40	Iniencephalus, spina bifida, talipes (stillborn).
17	3	♀	35	Anencephalus, spina bifida, talipes (stillborn).
18	2	♂	36	(Stillborn).
19	2	♂	27	Mongolism, spina bifida, harelip and cleft palate (stillborn).
20	11	♂	39	(Stillborn).
21	4	♂	36	—
22	4	♀	42	Ectopia vesicae, uterus bicornis, malrotation of gut, bilateral harelip and cleft palate, polydactyly, defects in skin of scalp (P.M.)
23	1	♂	25	(Twin).
24	1	♀	24	Anencephalus, spina bifida (stillborn).
25	3	♀	25	Cervico-dorsal meningomyelocele, Arnold Chiari malformation, cleft palate, diverticulum of diaphragm (stillborn—P.M.).
26	2	♀	26	Atresia of oesophagus with small tracheo-oesophageal fistula, absence of both radii and thumbs, absence of left half of diaphragm, hypoplasia of left lung, malrotation of gut (P.M.).
27	1	♂	20	Anencephalus (stillborn).
28	2	♀	20	'Deformed spine' (stillborn).
29	1	♀	19	Anencephalus (stillborn).
30	1	♀	27	Anencephalus, spina bifida (stillborn).
31	2	♀	23	(Stillborn).
32	3	♂	42	Malrotation of gut, atresia of distal small intestine and proximal large intestine, internal hydrocephalus, right talipes equino-varus (P.M.)
33	2	♂	40	(Stillborn).
34	2	♀	32	Anencephalus (stillborn).
35	1	♂	25	Anencephalus (stillborn).
36	3	♀	27	Arnold Chiari malformation, poor development of face, talipes equino-varus (stillborn).

APPENDIX—*Continued*

NO. OF FRATERNITY	BIRTH ORDER	SEX	AGE OF MOTHER	ASSOCIATED MALFORMATIONS
37	2	♀	31	Ectopia vesicae, part of pelvis absent, uterus didelphys, sacral teratoma (P.M.).
38	1	♂	22	—
39	1	♀	34	Bilateral defect of diaphragm, absence of one lung (stillborn—P.M.).
40	2	♀	32	(Stillborn).
41	3	♂	34	Primitive midgut.
42	2	♂	27	—
43	1	♂	26	Ectopia vesicae, persistent cloaca, absent large intestine, persistent omphalo-intestinal duct (P.M.).
44	2	♀	28	Anencephalus (stillborn).
45	10	♂	39	(Stillborn).
46	4	♀	33	—
47	4	♂	38	Mongolism, cleft palate, persistent common mesentery (P.M.).
48	1	♂	31	—
49	2	♂	36	—
50	1	♀	34	—
51	2	♂	27	Ectopia vesicae.
52	2	♀	26	'General disproportion', bilateral talipes.
53	2	♂	26	—
54	1	♀	26	(Stillborn, twin).
55	3	♀	28	Anencephalus (stillborn).
56	2	♀	26	—
57	4	♀	43	Diaphragmatic hernia, deficiency of pericardium (P.M.).
58	4	♂	32	Anencephalus and spina bifida (stillborn).
59	5	♂	37	Hydrocephalus, 'malformation of both hands' (stillborn).
60	1	♀	19	—
61	1	♂	21	—
62	1	♂	38	(Stillborn).
63	1	♂	20	Anencephalus (stillborn).
64	1	♂	21	'Body appeared to be rotated through half a circle at waist.'
65	3	(?)	34	Absence of external genitalia, rudimentary opening of bowel into bladder, lumbo-sacral meningocele, bilateral talipes calcaneo-valgus (stillborn—P.M.).
66	5	♀	29	Anencephalus (stillborn).
67	3	♀	28	Anencephalus and spina bifida (stillborn).
68	?	♀	?	—

The Incidence of Harelip and Cleft Palate Related to Birth Rank and Maternal Age

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THE POSSIBILITY that manifestation of harelip and cleft palate is influenced by maternal age and birth order was suggested by the observation that in a highly inbred strain of mice manifestation was more complete in offspring of young mothers (Reed, 1936). Results of investigation in man have hitherto been inconclusive or negative. Using the Greenwood-Yule method Fogh-Andersen (1942) noted no difference between observed and expected distributions by birth rank of 153 patients from fraternities for which information was considered complete. Results of examination of maternal age were also negative, but are less reliable since he relied upon a comparison of mean age in a selected series of cases and in all births delivered in Denmark during one year. Grace (1943) found no difference between the percentages of first born in 250 cases of harelip and cleft palate, and in all births in the state of Pennsylvania. Examination of maternal age was unsatisfactory, since information was not available for normal births. Tiedemann (1949) compared 676 affected of all ages, for whom data were collected by postal enquiry from health centres and schools in fifteen German provinces, with legitimate births delivered in Bayern during one year. He reported an excess of affected in the lower birth ranks and maternal ages, but for obvious reasons the data are unsatisfactory.

In this communication we present evidence that in man the incidence of harelip, and of harelip associated with cleft palate, is unrelated to birth order, but increases with maternal age. The incidence of cleft palate not associated with harelip appears to be independent of both maternal age and birth order.

We have attempted to collect all cases of harelip and cleft palate born in the years 1940–50 to mothers domiciled within the administrative boundary of Birmingham. Sources of data were (a) clinical and post mortem records of all maternity, paediatric and general hospitals in the city, (b) the registers of stillbirths and infants deaths of the local authority. Children treated in Birmingham hospitals but not born in this period were excluded, as were children of mothers not resident in Birmingham. 285 cases of harelip and cleft palate were identified in a population of 218,693 births, an incidence of 1.30 per thousand total births. This is in general agreement with other recent estimates of incidence: 1.50 (Fogh-Andersen, 1942); 1.23 (Grace, 1943); 1.30 (Mueller, 1946); 1.07 (Hixon, 1951) and 1.31 (Ivy, 1951).

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For cases in which information about birth rank and maternal age was not available in existing records it was sought, first by postal enquiry, and finally by home visit. By these methods birth rank was recorded for 276 (96.8%) of the 285 patients, and maternal age for 248 (87.0%). A control series was prepared by selecting from local authority registers every 200th live birth and stillbirth delivered in the city during the same years. Information about this series had been obtained during previous investigations (McKeown, Mac Mahon and Record, 1951) and it was only necessary to extend the series to cover the last year. Birth rank and maternal age are known for 1105 (93.8%) of the 1178 controls delivered in the period 1940–50.

BIRTH RANK AND MATERNAL AGE

Distributions of affected and controls by birth rank and maternal age are given in full in table 1, affected being classified under (a) harelip, (b) cleft palate, and (c) harelip with cleft palate. Percentage distributions by birth rank are compared in table 2, and by maternal age in table 3. There are no significant differences between proportions of affected (all types) and controls in each birth rank; the proportions in the first two birth ranks are lower for harelip and for harelip with cleft palate than for cleft palate, but the differences are not significant. There are however substantial differences between the percentage distributions of affected and controls by maternal age, the proportion of affected being low in the lower maternal age groups, and high in the upper age groups. These differences are due to patients with harelip, or with harelip and cleft palate; the percentage distribution of patients with cleft palate does not differ significantly from that of controls. When cases of cleft palate are excluded, the difference between the proportions of affected and of controls in the age group "38 and over" is 9.3 ± 2.6; in the same age group the difference between proportions of affected with harelip (with or without cleft palate), and of affected with cleft palate only, is 9.9 ± 4.6.

Table 4 gives the incidence of affected with harelip (with or without cleft palate) per thousand total births of the same birth rank and maternal age. (The distribution of the population of 218,693 related total births has been estimated from the known distribution by birth rank and maternal age of the 1105 controls.) Incidence increases with maternal age, from 0.37 at ages "under 23" to 1.41 at ages "38 and over" (column totals) but appears to be unrelated to birth rank (row totals). When birth rank is fixed the association with age is reasonably consistent (reading along the rows), but when age is fixed there is no consistent association with birth rank (reading down the columns).

Since harelip and cleft palate are sometimes associated with other malformations whose incidence increases with maternal age (for example mongolism), we have compared the percentage distribution of 121 affected (with harelip, with or without cleft palate) who exhibited no other malformation, with the

TABLE 1. NUMBERS OF AFFECTED AND CONTROLS AT DIFFERENT BIRTH RANKS AND MATERNAL AGES

MATERNAL AGE (YEARS)	BIRTH RANK																				TOTAL			
	1				2				3				4				5 and over							
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
Under 23	4	10	3	124	—	1	4	30	1	—	—	8	—	—	—	1	—	—	—	—	5	11	7	163
23–27	6	11	18	168	8	12	7	121	1	5	2	37	—	2	1	17	—	—	—	6	15	30	28	349
28–32	6	8	8	78	2	10	11	108	3	3	7	58	3	2	2	32	2	2	2	22	16	25	30	298
33–37	1	5	2	26	1	12	7	59	3	1	1	38	2	1	3	27	1	2	3	45	8	21	16	195
38 & over	1	—	1	6	5	1	2	16	2	1	3	13	2	—	4	22	2	6	6	43	12	8	16	100
Unknown	1	6	3	—	—	3	5	—	2	2	—	—	3	—	—	—	1	2	—	—	7	13	8	—
Total	19	40	35	402	16	39	36	334	12	12	13	154	10	5	10	99	6	12	11	116	63	108	105	1105

(a) Harelip (For 3 of 66 cases birth rank and maternal age are unknown).
(b) Cleft palate (For 6 of 114 cases birth rank and maternal age are unknown).
(c) Harelip with cleft palate.
(d) Controls (For 73 of 1178 controls birth rank and maternal age are unknown).

TABLE 2. DISTRIBUTIONS OF AFFECTED AND CONTROLS BY BIRTH RANK

BIRTH RANK	AFFECTED								CONTROLS (b)		DIFFERENCE IN PERCENTAGES (a) − (b)
	Harelip		Cleft Palate		Harelip with Cleft Palate		Total (a)				
	No.	%	No.	%	No.	%	No.	%	No.	%	
1	(19)	30.2	(40)	37.1	(35)	33.3	(94)	34.1	(402)	36.4	−2.3 ± 3.2
2	(16)	25.4	(39)	36.1	(36)	34.3	(91)	33.0	(334)	30.2	+2.8 ± 3.1
3	(12)	19.0	(12)	11.1	(13)	12.4	(37)	13.4	(154)	13.9	−0.5 ± 2.3
4	(10)	15.9	(5)	4.6	(10)	9.5	(25)	9.0	(99)	9.0	0 ± 1.9
5 and over	(6)	9.5	(12)	11.1	(11)	10.5	(29)	10.5	(116)	10.5	0 ± 2.1
Total..................	(63)	100.0	(108)	100.0	(105)	100.0	(276)	100.0	(1105)	100.0	—

Birth rank is unknown for 9 (3.2%) of 285 affected and for 73 (6.2%) of 1178 controls.

TABLE 3. DISTRIBUTIONS OF AFFECTED AND CONTROLS BY MATERNAL AGE

MATERNAL AGE (YEARS)	AFFECTED										DIFFERENCE IN PERCENTAGES (a) − (b)
	Harelip		Cleft Palate		Harelip with cleft palate		Total (a)		Controls (b)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Under 23	(5)	8.9	(11)	11.6	(7)	7.2	(23)	9.3	(163)	14.8	−5.5 ± 2.4*
23–27	(15)	26.8	(30)	31.6	(28)	28.9	(73)	29.4	(349)	31.6	−2.2 ± 3.3
28–32	(16)	28.6	(25)	26.3	(30)	30.9	(71)	28.6	(298)	27.0	+1.6 ± 3.1
33–37	(8)	14.3	(21)	22.1	(16)	16.5	(45)	18.2	(195)	17.6	+0.6 ± 2.7
38 and over	(12)	21.4	(8)	8.4	(16)	16.5	(36)	14.5	(100)	9.0	+5.5 ± 2.1*
Total	(56)	100.0	(95)	100.0	(97)	100.0	(248)	100.0	(1105)	100.0	

Maternal age is unknown for 37 (13.0%) of 285 patients, and for 73 (6.2%) of 1178 controls.
* Difference exceeds twice its standard error.

distribution of the controls. The proportion of affected in the age group "38 and over" (15.7%) is higher than that of controls (difference 6.7 ± 2.8). It is concluded that the increase in incidence of harelip (with or without cleft palate) with maternal age exists independently of association with other malformations.

TABLE 4. INCIDENCE OF AFFECTED WITH HARELIP (WITH OR WITHOUT CLEFT PALATE) RELATED TO BIRTH RANK AND MATERNAL AGE

BIRTH RANK	MATERNAL AGE (YEARS)										TOTAL	
	Under 23		23–27		28–32		33–37		38 & over			
	No.	Incidence	No.	Incidence	No.	Incidence	No.	Incidence	No.	Incidence	No.	Incidence
1	(7)	0.29	(24)	0.72	(14)	0.91	(3)	0.58	(2)	1.68	(50)	0.63
2	(4)	0.67	(15)	0.63	(13)	0.61	(8)	0.69	(7)	2.21	(47)	0.71
3	(1)	—	(3)	0.41	(10)	0.87	(4)	0.53	(5)	1.94	(23)	0.75
4	(0)	—	(1)	—	(5)	0.79	(5)	0.94	(6)	1.38	(17)	0.87
5 and over	(0)	—	(0)	—	(4)	0.92	(4)	0.45	(8)	0.94	(16)	0.70
Total...	(12)	0.37	(43)	0.62	(46)	0.78	(24)	0.62	(28)	1.41	(153)	0.70

Incidence is expressed as the number of affected individuals per thousand total births of the same birth rank and maternal age.

TABLE 5. SEX RATIOS OF AFFECTED

MALFORMATION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	PERCENTAGE MALE
Harelip	66	23.2	60.6
Cleft palate	114	40.0	41.2
Harelip with cleft palate	105	36.8	59.0
Total	285	100.0	52.3

SEX RATIO

Table 5 gives sex ratios of the three groups of malformation. The results are reasonably consistent with those recorded by Fogh-Andersen (1942), Ivy (1951), and Hixon (1951), who also noted an excess of males among affected with harelip, or with harelip and cleft palate, and an excess of females among affected with cleft palate only.

ASSOCIATED MALFORMATIONS

Table 6 gives details of other malformations exhibited by affected. The incidence of other malformations is 15.8% (harelip 9.1, cleft palate 14.9, harelip with cleft palate 21.0). This is higher than an estimate of 4.9% derived from

Fogh-Andersen's data (harelip 2.4, cleft palate 7.4, harelip with cleft palate 4.8). Fogh-Andersen's cases excluded many stillbirths and early deaths, and hence it is probable that his estimates considerably understate the frequency with which other abnormalities, particularly serious abnormalities, are associated with harelip and cleft palate.

TABLE 6. MALFORMATIONS ASSOCIATED WITH HARELIP AND CLEFT PALATE

ASSOCIATED MALFORMATION	HARELIP (66 CASES)	CLEFT PALATE (114 CASES)	HARELIP WITH CLEFT PALATE (105 CASES)	TOTAL (285 CASES)
Anencephalus	—	—	3	3
Anencephalus with spina bifida	—	1	—	1
Spina bifida	2	—	—	2
Microcephalus	—	—	3	3
Hydrocephalus	—	—	1	1
Mongolism	—	1	1	2
Mongolism with hypospadias & syndactyly	—	1	—	1
Mongolism with congenital heart disease	—	—	1	1
Congenital heart disease	1	1	3	5
Congenital heart disease with syndactyly or polydactyly	1	2	1	4
Exomphalos	—	2	—	2
Exomphalos with microcephalus & polydactyly	—	—	1	1
Micrognathia	—	2	—	2
Malformation of tongue	1	1	—	2
Syndactyly	—	1	—	1
Adactyly	—	—	1	1
Deformity of toe	—	—	1	1
Deformity of lower jaw	—	1	—	1
Depressed sternum	—	—	1	1
Talipes	—	1	—	1
Klippel Feil syndrome	—	1	—	1
Achondroplasia	—	—	1	1
Hypospadias	—	—	1	1
Diaphragmatic hernia	—	1	—	1
Bilateral accessory auricles	—	—	1	1
Unspecified deformities	1	1	2	4
Total	6	17	22	45
Percentage incidence	9.1	14.9	21.0	15.8

SUMMARY

1. An attempt has been made to collect all cases of harelip and cleft palate born to Birmingham mothers in the years 1940–50. 285 cases were identified in a population of 218,693 births, an incidence of 1.30 per thousand total births.

2. Birth rank was recorded in 276 (96.8%) of the 285 affected, and maternal

age in 248 (87.0%). The same information was available for 1105 (93.8%) of 1178 control births, selected by taking every 200th name from the registers of live births and stillbirths delivered in the city during the same years.

3. It is shown that the incidence of harelip, and of harelip associated with cleft palate, is unrelated to birth rank, but increases with maternal age (from 0.37 per thousand total births at ages "under 23" to 1.41 per thousand at ages "38 and over"). The incidence of cleft palate not associated with harelip appears to be independent of both maternal age and birth order.

4. For harelip, cleft palate, and harelip with cleft palate respectively: (a) Sex ratios (expressed as the percentage of males) are 60.6, 41.2, and 59.0; (b) The percentage incidence of associated malformations is 9.1, 14.9 and 21.0.

These results are consistent with Fogh-Andersen's report (1942) that in several respects harelip and harelip with cleft palate are biologically similar, and differ from cleft palate not associated with harelip.

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For case records we are indebted to the staffs of all Birmingham hospitals, in particular of the Children's Hospital, and to the Maternity and Child Welfare Department of the city. We are grateful to Miss M. S. Gradwell for assistance in the collection of material and analysis of the data. Dr. MacMahon is in receipt of a grant from the Medical Research Council.

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BOOK REVIEWS

Die Entwicklungstörungen der Extremitäten

BY A. WERTHEMANN, Berlin: JULIUS SPRINGER, Verlag, 1952, Pp. 424 Ladenpreis: DM 98—Canzleinen DM 103.60

THIS handbook contribution by the pathology professor of Basel University is the result of 15 years of scholarly work, based on personal observations and on extensive study of the literature. As the author states on pp. 226 and 408, the interest of this monograph is primarily focused on anatomy, embryology and special pathology and aims at explaining the formal origin of the malformations of the limbs. Most of the material is presented on the macroscopic level, with profuse illustration by excellent photographs and roentgenograms. This makes the text important also to clinicians who study the normal and abnormal development of the human fetus and child, such as obstetricians, pediatricians and orthopedic surgeons. As a pediatrician, the present reviewer would feel that the book's clinical usefulness might be increased by being more specific on age, weight and size of fetuses, newborns, infants and children described in the legends and text, as that would facilitate the interpretation of x-rays for osseous maturation and help avoid ambiguity and doubts in the use of the material.

The subject matter is divided into four parts. In the first part, or "Introduction", besides notes on human and experimental embryology, a discussion of the causal origin of limb defects is presented. This is where many of the well-known genetic problems appear in summary, the details being scattered all over the text in the form of personal pedigree observations and, mostly, of references to the inheritance literature.

The second and third parts deal, respectively, with "the deviations of the skeletal anlage" and "the malformations based on disturbances of the primitive soft-tissue plate." Subsections of part two attempt to distinguish between (1) numerical plus and minus variations of osseous "rays" and (2) disturbances of epiphyseal and joint development. In the section on joints such important anomalies as congenital dislocation of the hip and congenital club foot are treated at great length. The association in part three of congenital localized gigantism with syndactylism and "lobster claw" would surprise those who think of the former in terms of von Recklinghausen's neurofibromatosis.

In the fourth part, under the title "Closing Remarks," there is hidden what, in the author's opinion, legitimately remains of "amniotic" constrictions and amputations. The famous paper by G. L. Streeter (1930) is not mentioned in this context.

On the whole, this monograph is a stupendous piece of searching scholarship, enhanced by a high quality printing job on the part of the illustrious Springer publishers. The book's price does not appear too high for that.

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Heredity in Bronchial Asthma

By Michael Schwartz, Copenhagen: Einar Munksgaard, 1952. Pp. 288.

This monograph is a contribution from The University Institute for Human Genetics, Copenhagen, Denmark. It constitutes Volume 29 of Opera Ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis.

Following a detailed historical review of topics such as "The Modern Concept of Allergy," "Heredity in Allergic Diseases" and "Allergic Reactions in Animals" the author presents his own investigations. In these he employed the statistical genealogical proband method of Weinberg (1931) which consists of a comparison of the incidence of the disease in question among the relatives of probands possessing the disease and the incidence among relatives of a control series of normal probands. The study comprises a total of 191 asthma probands, 200 control probands and 50 probands with baker's asthma.

Among the 9 conclusions drawn by the author the following 4 may be selected: (1) Bronchial asthma is a hereditary disease regardless of whether or not it is of definite allergic origin. (2) A genetic relationship exists between asthma and: vasomotor rhinitis, Besnier's prurigo, and—presumably– hay fever. (3) In all probability the mode of inheritance of bronchial asthma is that of an autosomal dominant with 40% penetrance; and (4) Contrary to what is generally believed, this study showed no genetic relationship between asthma (vasomotor rhinitis, etc.) and the diseases: eczema, migraine, urticaria, Quincke's oedema, epilepsy, ichthyosis, gastrointestinal allergy and psoriasis.

The investigation appears to have been carefully planned and executed, and all of the conclusions seem to be warranted. One point of special interest is that the four allergies which were found to be inherited and related, correspond to those which have long been called by Coca the atopic diseases. The author, however, questions the need or desirability of a single name for the four diseases.

The monograph was originally written in Danish, but is translated into English. The translation is that of Anna La Cour and is well done. Only in a few instances is the genetic meaning of a statement somewhat obscure.

All in all the monograph represents another very fine contribution to human genetic literature from the Institute of Human Genetics of which Professor Tage Kemp, M.D., is the Head.

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BIBLIOGRAPHY OF HUMAN GENETICS

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THIS SECTION is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made, and is being made to make the list complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above, any recent reference which has been missed or any current reference which it seems probable may be missed as a result of its appearance in a journal which probably is not systematically covered by the bibliographic editor. If a reference to an article is sent in be sure that it is complete with respect to name of author(s), year of publication, title of article, name of journal, volume number, and first and last page numbers. If the reference is to a book be sure that it includes name of author(s), year of publication, title, name of publisher, place of publication, and number of pages.

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